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Gastric Intestinal Metaplasia Is the Most Common Histopathological Phenotype among Endoscopically Diagnosed Atrophic Gastritis Patients in North-East China

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Abstract

Background: Gastric cancer and gastric precancerous lesions are highly prevalent in China. However, prevalence of the different precancerous lesions has not been reported from the north-east region of China. Detection of precancerous gastric lesions at an early stage complemented with a follow-up strategy for high risk groups would probably aid in declining the mortality rate in patients with gastric cancer. *Helicobacter pylori* infection, salt intake, smoking, alcohol, family history of gastric cancer, atrophic gastritis and intestinal metaplasia are established risk factors of gastric cancer. The aim of this study was to evaluate the frequency of various histopathological phenotypes among atrophic gastritis patients in this region and to report if gender and increasing age carry risk in the development of these lesions. **Methods:** This retrospective study was conducted on 518 patients with endoscopic diagnosis of atrophic gastritis. Using the patient number in database, histopathological diagnosis of the biopsy specimen of all patients was recorded. All biopsy specimens were assessed for the presence of inflammation, atrophic gastritis, metaplasia and/or dysplasia. **Results:** Intestinal metaplasia was observed in 67.38% of patients. Dysplasia and atrophy were present in 9.46% and 3.67% patients, respectively. Gender and increasing age were not found to be risk factors for intestinal metaplasia, dysplasia and atrophic gastritis (p-values 0.08, 0.43, 0.297 and 0.98, 0.20, 0.54; respectively). 19.49% subjects showed inflammatory activity which was significantly associated with female gender (P = 0.0008). **Conclusion:** Intestinal metaplasia was the most histopathological phenotype among endoscopically diagnosed atrophic gastritis patients. Large-population based on prospective studies should be designed to determine prevalence of precancerous lesions and the risk factors involved in

the progression of these lesions in our region.

Keywords

Atrophic Gastritis, Endoscopy, Metaplasia, Gastric Cancer

1. Introduction

Gastric cancer (GC) is the fourth most common cancer worldwide [1] while it ranks the third most common cancer in China [2]. GC remains the second leading cause of cancer-related death around the globe [3], despite tremendous advancement in diagnostic and therapeutic endoscopy techniques. Detection of precancerous gastric lesions at an early stage complemented with a follow-up strategy for high risk groups would probably aid in declining the mortality rate in GC patients. *Helicobacter pylori* (*H. pylori*) infection, salt intake, smoking, alcohol, family history of gastric cancer, atrophic gastritis (AG) and intestinal metaplasia (IM) are established risk factors of gastric cancer [4].

Atrophic gastritis, defined as the loss of glands [5] is well known as a risk factor of gastric cancer. Endoscopic AG is characterized by the loss of gastric mucosal gland and submucosal vascular pattern visibility. AG is usually diagnosed at endoscopy in Asian countries—in particular—East Asian countries while histological examination of biopsy obtained during endoscopy is a necessity for AG diagnosis in the western countries. Marques-Silva *et al.* [6] carried out a meta-analysis to study the distribution of precancerous gastric lesions around the globe. The prevalence of atrophic gastritis and IM in the worldwide population was 33.4% and 25% respectively, whereas extensive IM was found in 13%. They further found that precancerous lesions—AG and IM—were more prevalent in countries with high incidence of gastric cancer. Chronic atrophic gastritis is highly prevalent in China [7] and has a 5-fold tendency to progress to malignancy [8].

To the best of our knowledge, this is the first study from North-East region of China to document the frequency of various precancerous lesions in atrophic gastritis patients. We also evaluated if gender and increasing age are associated with the development of gastric precancerous lesions.

2. Methods

This retrospective study was conducted on 518 patients with endoscopic diagnosis of AG, from January 2012 to November 2014, at the Department of Gastroenterology and Endoscopy Center, First Hospital of Jilin University, Changchun, China. Demographic data of inducted patients was retrieved by observing the patients electronic record in the database. Patients whose presenting history revealed active GI bleeding and/or use of proton pump inhibitor/H2 receptor antagonist were not inducted in the study. The Ethics Committee of our hospital approved the study.

One biopsy was taken from the corpus while two biopsies were taken from antrum of all study subjects. Biopsy specimens were placed in vials containing 10% buffered formalin solution. Slides were stained with hematoxylin and eosin. Biopsy specimens were examined by senior pathologist specialized in gastric mucosal abnormalities. All specimens were assessed for the presence of inflammation, atrophic gastritis, metaplasia and/or dysplasia.

Statistical Analysis

Descriptive statistics for continuous variables (characteristics) were presented as mean, standard deviation, and minimum and maximum values. Multivariate logistic regression was used to determine association of risk factors (gender and increasing age) with the precancerous lesions. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. In addition, Fisher's exact test was performed to compare two proportions in groups. A P value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Basic Characteristics of Patients and Pathology Findings

518 patients (196 females and 322 males) were diagnosed with atrophic gastritis at endoscopy. Age ranged from 18 to 90 years while mean age was 60.54 years (±10.97 SD). After retrieving the pathological results from the database, histopathological phenotypes among endoscopically diagnosed AG patients were divided into four groups—metaplasia, dysplasia, AG and inflammatory activity (Figure 1). Patient demographics categorized in different group are shown in Table 1.

Of the 349 IM patients, 23 had atrophy and 119 had dysplasia but none of

Table 1. Demographics of study population.

	Intestinal Metaplasia	Dysplasia	Atrophic Gastritis	Inflammatory Activity	Total N = 518
Gender					
Male	226	33	14	48	322
Female	123	16	5	53	196
Age					
≤40	8	3	1	3	15
41 - 50	57	7	0	18	82
51 - 60	107	21	5	27	160
61 - 70	113	9	9	30	161
71 - 80	57	9	4	17	87
>80	7	0	0	6	13

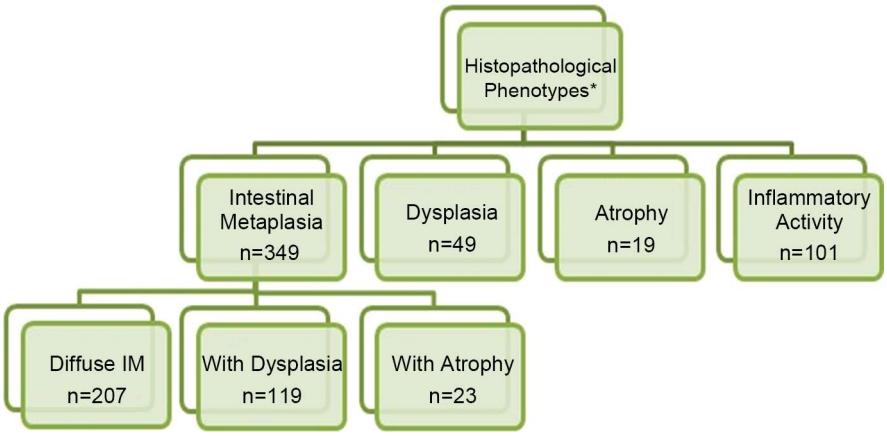

Figure 1. Classification of histopathological phenotypes among endoscopically diagnosed atrophic gastritis patients. IM: Intestinal Metaplasia; *Observed in 518 patients diagnosed with atrophic gastritis at endoscopy.

Table 2. Frequency of atrophy and dysplasia according to the presence and absence of intestinal metaplasia.

		Intestinal Metaplasia		Fisher Exact Test
		Negative N = 169	Positive N = 349	P value
Atrophy	Positive	19	23	0.085
	Negative	150	326	
Dysplasia	Positive	49	119	0.271
	Negative	120	230	

these lesions was found to be correlated with IM (P = 0.085 and P = 0.271, respectively) (Table 2).

3.2. Distribution of Age and Gender in Gastric Precancerous Lesions

The most common lesion was Gastric IM observed in 67.38% of patients. Among the patients diagnosed with IM, 64.8% were male while 35.2% were female. IM increased with increase in age until 70 years (from 2.3% in those less than 40 years of age to 63.04% in those between 50 and 70) (Figure 2). Dysplasia and Atrophy were present in 9.46% and 3.67% patients, respectively. Both lesions were common in male as compared with female. Dysplasia was most common between age 51 and 60 (42.9%) while diffuse AG at histology was common between ages 60 and 70 (Figure 2). However, multivariate analysis did not show any significant association of male gender and increasing age with the precancerous lesions—IM, AG and dysplasia as illustrated in Table 3 and Table 4.

3.3. Inflammatory Activity in Biopsied Samples of AG Patients

Inflammatory (neutrophilic) activity was observed in 101 (19.49%) subjects and

was significantly correlated with female gender (OR = 2.12; 95% CI = 1.36 - 3.28, P = 0.0008). Most of these patients were between 50 and 70 years of age (56.43%). However, in logistic regression, no significant association was found between increasing age and inflammatory activity as depicted in Table 4.

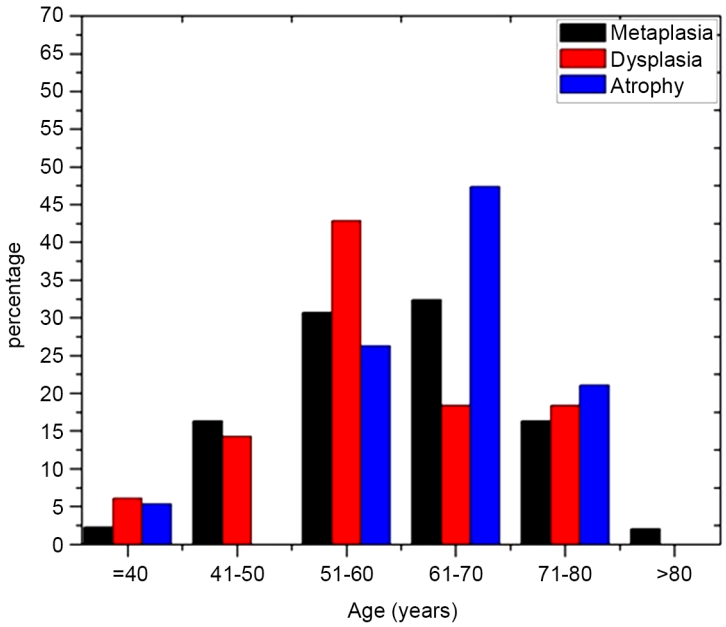

Figure 2. The percentage positivity of intestinal metaplasia, dysplasia and atrophy in 518 cases of atrophic gastritis (endoscopic) according to age group.

Table 3. Associated odds ratio for gender and age in intestinal metaplasia and dysplasia.

Variable	Intestinal Metaplasia			Dysplasia		
	Negative	Positive	OR (95% CI)	Negative	Positive	OR (95% CI)
Gender						
Male	96	226	1	289	33	1
Female	73	123	0.72 (0.49 - 1.04)	180	16	0.78 (0.42 - 1.46)
P value			0.08			0.43
Age						
≤40	7	8	1	12	3	1
41 - 50	25	57	1.995 (0.65 - 6.10)	75	7	0.37 (0.09 - 1.65)
51 - 60	53	107	1.77 (0.61 - 5.13)	139	21	0.60 (0.16 - 2.32)
61 - 70	48	113	2.06 (0.71 - 6.00)	152	9	0.24 (0.06 - 0.99)
71 - 80	30	57	1.66 (0.55 - 5.03)	78	9	0.46 (0.11 - 1.95)
>80	6		1.02 (0.23 - 4.53)	13	0	0.13 (0.01 - 2.83)
P value	7		0.98			0.20

OR: odds ratio; CI, confidence interval.

Table 4. Associated odds ratio for gender and age in inflammatory activity and atrophy.

Variable	Intestinal Metaplasia			Dysplasia		
	Negative	Positive	OR (95% CI)	Negative	Positive	OR (95% CI)
Gender						
Male	274	48	1	308	14	1
Female	143	53	2.12 (1.36 - 3.28)	191	5	0.58 (0.20-1.63)
P value			0.0008			0.297
Age						
≤40	12	3	1	14	1	1
41 - 50	64	18	1.13 (0.29 - 4.42)	82	0	0.06 (0.002 - 1.51)
51 - 60	133	27	0.81 (0.22 - 3.07)	155	5	0.45 (0.05 - 4.14)
61 - 70	131	30	0.92 (0.24 - 3.45)	152	9	0.83 (0.098 - 7.03)
71 - 80	70	17	0.97 (0.25 - 3.83)	83	4	0.68 (0.07 - 6.49)
>80	7	6	3.43 (0.65 - 18.22)	13	0	0.36 (0.01 - 9.57)
P value			0.15			0.54

OR: odds ratio; CI, confidence interval.

4. Discussion

Gastric Cancer is usually preceded by a cascade of lesions from non-atrophic gastritis to atrophic gastritis (AG), intestinal metaplasia (IM), dysplasia and finally carcinoma [9]. *Helicobacter Pylori* is the most common causative agent for the development of this cascade and therefore, the bacterium is classified as a Class I carcinogen by the International Agency for Research on Cancer of the World Health Organization [10]. Atrophic Gastritis and Gastric IM are well established as premalignant lesions in the literature [11] [12] [13] [14]. Atrophic gastritis is characterized by loss of normal architecture of gastric mucosa while in intestinal metaplasia, the normal gastric glands are replaced by glands that morphologically and histologically resemble those, found in the intestine.

IM is much more prevalent in East Asia, as compared with rest of the world. In our study, gastric IM was the most common lesion (67.38%) observed in the biopsies retrieved from endoscopically diagnosed AG patients. This high frequency of IM was consistent with a recent published retrospective study from South China [15]. Chen *et al.* [15] inducted 3969 patients endoscopically diagnosed with AG. One or two biopsies were taken from the antrum of all subjects. IM was present in 84.33% of these patients with IM correlating significantly with the severity of AG. In Korea, prevalence of gastric intestinal metaplasia was found to be 42.5% and 32.7% in antrum and corpus, respectively [16].

In a large multicenter study from Japan [17], prevalence of atrophic gastritis and IM was much higher in *H. pylori* infected patients compared with uninfected

patients (OR = 44.8; 95% CI = 34.7 - 57.8 and OR = 11.5; 95% CI = 8.5 - 15.5, respectively). In a study from Nigeria [18], gastric intestinal metaplasia was the most common lesion observed in gastro duodenal biopsies followed by AG and dysplasia. Eighty percent of the study population was positive for *H. pylori*, thus signifying a strong association between *H. pylori* and IM in agreement with the aforementioned study from Japan. In contrast, low prevalence of *H. pylori* in atrophic mucosa have been reported in the literature [19] [20]. Our study was confined to only patients with atrophy at endoscopy and biopsy samples retrieved from study subjects were not assessed for *H. pylori* presuming for low prevalence of *H. pylori* in atrophic gastritis.

A study from USA [21] reported that prevalence of gastric intestinal metaplasia was 15% among the 437 patients who had gastric biopsies performed. Olmez *et al.* [22] reported that, among the 4050 patients who had gastric biopsies performed, 560 were found to have gastric IM and they observed that the overall prevalence was 13.8% with IM Type III being the most prevalent among the IM subjects. A study from Romania [23] reported that the frequency of intestinal metaplasia was 61.6% in patients suffering from chronic gastritis, most of the cases presented with complete type IM.

At our institution, IM subtyping is not routinely practiced and extension of metaplastic change is generally observed in gastric mucosal samples. Conflicting data is found in the literature for subtyping IM and therefore, it is not widely practiced. Some authors describe a positive effect of typing IM and concluded that IM Type III carries the highest risk for developing gastric cancer whilst others refute it [24] [25] [26] [27]. On the other hand, extension of atrophic and metaplastic lesions is well accepted as a determinant for neoplastic changes and various guidelines exist to evaluate the extension of atrophy and/or IM [14] [28] [29]. The European Society of Gastrointestinal Endoscopy and other European academic societies, recommended guidelines to assess extent of atrophy and/or IM rather IM subtyping as an indicator for the surveillance of patients with atrophic gastritis and/or IM [30].

Increasing age and male gender have been reported to be significantly related to development of intestinal metaplasia [16] [31] [32]. On the other hand, IM was predominant in female gender as compared with male and the difference was statistically significant in a study reported from USA [19]. In our study, IM was more common in males than females but the difference was not statistically significant (OR = 0.72; CI = 0.49 - 1.04; $P > 0.05$). In addition, increasing age was NOT found to be a risk factor for the development of IM ($P = 0.98$). The contradictory results may be attributed to geographical variations and difference in the size of study population.

Fragments from mucosa of 101 patients showed inflammatory (neutrophilic) activity under microscope. Interestingly, it was significantly related with female gender but not with age.

We could not evaluate *H. pylori* status in the study population. However, the bacterium is highly prevalent in China [33] and we assume that the inflammatory

activity will most likely be due to presence of *H. pylori* that has the tendency to lead to neutrophilic activation and chronic gastritis [34].

The limitations of this study are as follows: first, study population was not large enough to give a better picture of the frequency of histopathological phenotypes among AG subjects. Secondly, in this study, *H. pylori* status for all the inducted patients could not be retrieved. Third, we only evaluated age and gender for extensive IM while other risk factors—such as alcohol consumption, smoking, increased BMI and high salt intake—are also known to contribute in the development of gastric precancerous lesions and gastric cancer.

5. Conclusion

In conclusion, our results show that histopathological diagnosis carries a pivotal role in patients with endoscopic diagnosis of AG. Our study highlighted the various histopathological phenotypes among AG patients with "gastric IM" being the most common lesion. More prospective cohort studies may be designed to: 1) determine the prevalence of gastric precancerous lesions in the general population in the North-East region; 2) evaluate relative risk of each individual phenotype to advance into a neoplasm which may aid in formulating surveillance guidelines for each phenotype; 3) identify the risk factors associated with the development of the precancerous lesions; and 4) determine the prevalence of *H. pylori* in the precancerous lesions in our region.

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