MARMARA
MEDICAL JOURNAL

Original Article

https://dergipark.org.tr/tr/pub/marumj

The natural course of gastric intestinal metaplasia in Turkish patients: A single-center observational cohort study

Coskun Ozer DEMIRTAS[1], Mesut KOLDAS[2], Metehan YILMAZ[2], Muhammed Zahid SAHIN[2], Muhammed Talha SOYKUVVET[2], Cigdem ATAIZI CELIKEL[3], Feyza GUNDUZ[1]

[1] Division of Gastroenterology, Department of Internal Medicine, School of Medicine, Marmara University, Istanbul, Turkey.
[2] School of Medicine, Marmara University, Istanbul, Turkey.
[3] Department of Pathology, School of Medicine, Marmara University, Istanbul, Turkey.

Corresponding Author: Feyza GUNDUZ
E-mail: drfgunduz@yahoo.com

Submitted: 01.03.2021 **Accepted:** 23.05.2021

ABSTRACT

Objective: Gastric intestinal metaplasia (GIM) is considered as a predisposing lesion for the development of gastric cancer and is recommended to be kept under surveillance in designated intervals. We aimed to assess the natural course of GIM in a large Turkish cohort.

Materials and Methods: We retrospectively reviewed findings from pathology reports of gastric biopsies conducted between 2011 to 2018 to reveal patients diagnosed with solitary GIM in their index pathology report. Progression of GIM was pre-defined as; low-grade dysplasia (LGD), high-grade dysplasia (HGD), or gastric malignancy.

Results: The median follow-up period of the study population was 34 (12-128) months. Out of 109 patients with GIM at the entry, 54 (49.6%) patients had stable GIM, whereas 53 (48.6%) cases had no signs of GIM at their final endoscopy. Only two (1.8%) patients progressed to LGD, but no HGD or malignancy was detected in the follow-up.

Conclusion: Although, considered as a premalignant lesion and offered surveillance globally, progression of GIM was very low in a large Turkish cohort. Further prospective studies in larger cohorts are required to enlighten the obscure strategies in the surveillance of gastric malignancy.

Keywords: Gastric intestinal metaplasia, Gastric cancer, Dysplasia, Surveillance

1. INTRODUCTION

Gastric intestinal metaplasia (GIM), defined as the replacement of the gastric mucosa by the intestinal mucosa, is a well-established precursor lesion for gastric cancer development [1]. The major risk factor for GIM development was shown to be *Helicobacter pylori (H. pylori)* infection with a 3 to 8 fold increased risk compared to the uninfected population [2]. The remaining potential risk factors are known as older age, male gender, low socioeconomic status, and smoking status [3,4]. Since, GIM is usually asymptomatic and found incidentally in patients undergoing upper gastrointestinal (GI) endoscopy, the exact incidence of GIM remains skeptical. The incidence of GIM was suggested to be about 25% for patients undergoing upper GI endoscopy, whereas it differed from 9% to 29.3% in previous reports from East Asia [5-7]. In 2015, the prevalence of GIM in Turkey was reported as 13.8% with the predominance of incomplete subtype [8].

Patients with GIM demonstrate a 6 to 9 fold higher risk of gastric cancer compared with the general population [9,10]. The development of gastric cancer is generally considered as a multistep process including sequential changes of the gastric mucosa from non-atrophic gastritis to atrophic gastritis, GIM, dysplasia, and finally cancer. *H. pylori* is generally thought to be responsible for pulling the trigger of this carcinogenic process [11]. However, it is still an undetermined issue as to whether all patients with GIM require a strict endoscopic surveillance program despite the fact that gastric cancer usually arises with

How to cite this article: Demirtas CO, Koldas M, Yilmaz M, et al. The natural course of gastric intestinal metaplasia in Turkish Patients: A single-center observational cohort study. Marmara Med J 2021; 34(3):229-233. doi: 10.5472/marumj.1013580

© 2021 Marmara University Press, All Rights Reserved
ISSN: 1309-9469

http://doi.org/10.5472/marumj.1013580
Marmara Med J 2021;34(3): 229-233

concomitant GIM [12]. In 2019, the updated international guideline (Management of precancerous conditions and lesions of the stomach-MAPS-II) recommended endoscopic surveillance for those with extensive GIM located in antrum and corpus as well, or single location but with a family history or incomplete subtype with persistent *H. pylori* gastritis [13]. However, even in those suggested subgroups, the majority remains stable or show regression that may be either true regression mainly related to *H. pylori* eradication or pseudo-regression due to sampling and interobserver variation in histologic examination [14].

The present study aimed to investigate the natural course of GIMs in Turkish patients for the first time and expose the proportion of patients with progression to dysplasia or invasive carcinoma. Moreover, the histological changes in the characteristics of GIM throughout the follow-up period are investigated as well.

2. MATERIALS and METHODS

Patient selection and data collection

We retrospectively reviewed findings from 22.465 pathology reports of gastric biopsies conducted between 2011 to 2018 to reveal patients diagnosed with GIM in their index pathology report (n=372). All upper GI procedures and histopathologic evaluation were performed at a tertiary center with a busy endoscopic practice. Patients lost to follow-up (n=203), having inconsistent surveillance intervals lower than one year (n=25), lack of data (n=15), low-grade dysplasia (LGD) (n=8), high-grade dysplasia (HGD) (n=1) or gastric malignancy (n=6) at the initial screening or gastrectomy operation at the entry (n=2) were excluded. As a result, all patients over the age of 18 with GIM in their index upper GI endoscopy pathology report who underwent at least one surveillance upper GI endoscopy after the index endoscopy (n=109) were included for the analysis. The flow diagram of the study is presented in Figure 1.

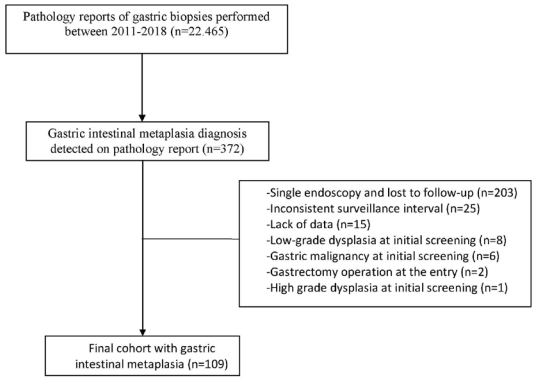

Figure 1. *Flow diagram of the study*

The demographics, details of initial upper GI endoscopy, number of biopsies taken, and histopathologic characteristics were provided from the electronic hospital database. The symptoms and/or findings leading to index upper GI endoscopy were mainly dyspepsia, epigastric pain, diarrhea, loss of weight, iron deficiency anemia, and a family history of GI malignancy.

Progression of GIM was defined as; LGD, HGD, or gastric malignancy. The follow-up time was calculated from the date of index endoscopy to the date of final endoscopy. Patients with the progression of GIM were censored for follow-up at the time of detection of progression, otherwise, patients were censored at the time of final upper GI endoscopy obtained from the hospital database.

Upper GI endoscopy procedure and histopathologic evaluation

All endoscopies were performed using a standard forward-viewing video-gastroscope (PENTAX Medical, New Jersey, USA). Both index endoscopies and surveillance endoscopies were performed by the experienced endoscopists in the same tertiary center using the local protocol with at least two biopsied samples from the antrum (including incisura angularis) and corpus. The number of biopsies may have increased based on the visible lesions observed in the upper GI endoscopy or the physician's preference.

Biopsy samples were fixed with formalin in paraffin blocks and stained with hematoxylin & eosin. All biopsy samples were evaluated by an experienced gastrointestinal pathologist who has experience for more than 10 years in this field.

The study followed the tenets of the Helsinki Declaration and it was approved by the local Ethics Committee (Protocol No: 09.2019.808) of Marmara University, School of Medicine. Owing to the retrospective nature of the study, the need for informed consent was waived.

Statistical analysis

The analysis was primarily descriptive. Data are reported as number (%) of patients unless indicated otherwise. All statistical analyses were conducted using the SPSS software version 20.0 (IBM, Armonk, NY, USA).

3. RESULTS

Through a careful investigation of 22.465 gastric pathology reports and exclusion consistent with the aforementioned criteria, 109 patients had GIM at their index endoscopy and were followed up for a period of 34 (12-128) months. Among them, 62 (56.9) were female and the mean age of the study population at the entry was 61.3 ± 11.6 years. The features of index endoscopies are presented in Table I. Diagnosis of index upper GI endoscopy was antral gastritis in the majority (n=74, 67.9%), followed by atrophic gastritis (n=17, 15.6%), pangastritis (n=5, 4.6%), erosive gastritis (n=5, 4.6%), antral ulcer (n=3, 2.8) and duodenal ulcer (n=3, 2.8). Only one (0.9%) patient was reported as normal upper GI endoscopy and one other (0.9%) had gastric polyp located in the antrum. The median number of biopsies taken in the index endoscopy was 2 [2-8]. The localization of GIM in the index endoscopy was dominantly

http://doi.org/10.5472/marumj.1013580
Marmara Med J 2021;34(3): 229-233

antrum (n=43, 39.4%), followed by corpus (n=13, 11.9%) and both of each (n=9, 8. 3%). The type of GIM was incomplete in 37 (33.9%), complete in 26 (23.9%), and the combination of both in 46 (42.2%) at the index endoscopy. The involvement pattern of GIM was focal in 72 (66.1%) patients and diffuse in 37 (33.9%) cases. Out of 109 analyzed patients, 29 (26.6%) had *H. pylori* at their index endoscopy.

Table I. *Endoscopic and histologic findings of patients at the entry and final*

	Initial Findings	Final Findings
Endoscopic diagnosis, *n (%)*		
Normal	1 (0.9)	-
Antral gastritis	74 (67.9)	73 (67)
Pangastritis	5 (4.6)	13 (11.9)
Atrophic gastritis	17 (15.6)	9 (8.3)
Erosive gastritis	5 (4.6)	7 (6.4)
Antral ulcer	3 (2.8)	1 (0.9)
Duodenal ulcer	3 (2.8)	2 (1.8)
Antral + Duodenal ulcer	-	1 (0.9)
Gastric polyp	1 (0.9)	3 (2.8)
Number of biopsy specimens, med (min-max)	2 (2-8)	2 (2-7)
Intestinal metaplasia localization, *n (%)*		
Antrum	43 (39.4)	29 (51.8)
Corpus	13 (11.9)	14 (25)
Antrum-corpus	9 (8.3)	4 (7.1)
Unspecified	44 (40.4)	9 (16.1)
Histologic duodenitis, n (%)	2 (1.8)	2 (1.8)
Histologic atrophy, n (%)	36 (33)	41 (37.6)
Histologic gastritis, n (%)	97 (89)	97 (89)
Helicobacter pylori, n (%)	29 (26.6)	9 (8.3)
Metaplasia type, n (%)		
None	-	53 (48.6)
Incomplete	37 (33.9)	12 (11)
Complete	26 (23.9)	22 (20.2)
Incomplete + Complete	46 (42.2)	22 (20.2)
Metaplasia involvement, n (%)		
Focal	72 (66.1)	42 (75)
Diffuse	37 (33.9)	14 (25)
Follicular hyperplasia, n (%)	26 (23.9)	25 (22.9)
Lymphoid aggregate, n (%)	14 (12.8)	16 (14.7)
Neuroendocrine cell hyperplasia, n (%)	6 (5.5)	3 (2.8)

Characteristics of the final endoscopies are presented in Table I as well. In the final endoscopies, the distribution of endoscopic diagnoses was quite similar with dominance of antral gastritis (n=73, 67%) followed by pangastritis (n=13, 11.9%), atrophic gastritis (n=9, 8.3%), erosive gastritis (n=7, 6.4%), antral and/or duodenal ulcer (n=4, 3.6%). Two more patients were found to have gastric polyps at their final endoscopies. The median number of biopsies taken in the final endoscopy was 2 [2-7]. The localization of GIM in the final endoscopy was dominantly antrum (n=29, 51.8%), followed by corpus (n=14, 25%) and both of each (n=4, 7.1%). Approximately, half of the study population (n=53, 48.6%) were found to have no GIM in their final endoscopy. The type of GIM in the remaining was as follows; complete in 22 (20.2%), incomplete in 12 (11%), and combination of both in 22 (20.2). The involvement pattern of GIM at the final endoscopy was focal in 42 (75%) patients and diffuse in 14 (25%) cases. The number of detected patients with *H. pylori* decreased to 9 (8.3%) in the final endoscopy, mainly due to treatment.

Fifty-four (49.6%) patients had stable GIM in a median follow-up period of 30 (12-97) months, whereas 53 (48.6%) cases had no signs of GIM at their final endoscopy in a median follow-up period of 39 (13-87) months (Figure 2). Out of 109 reviewed patients with solitary GIM at the entry, only two (1.8%) patients were progressed to LGD. Case-1 with detected LGD in her final endoscopy recruited to a repeat endoscopy in the following 6 months and 1 year and no signs of LGD were observed in both. On the other hand, Case-2 with detected LGD underwent endoscopic ultrasonography due to suspicious antral ulcer 3 months later and was biopsied again under endoscopic ultrasound guidance. The evaluation of the biopsy sample obtained under endoscopic ultrasound guidance showed that the LGD was regressed as well, and no signs of LGD was observed in the subsequent endoscopies. The details of the two cases with detected LGD is exhibited in Table II.

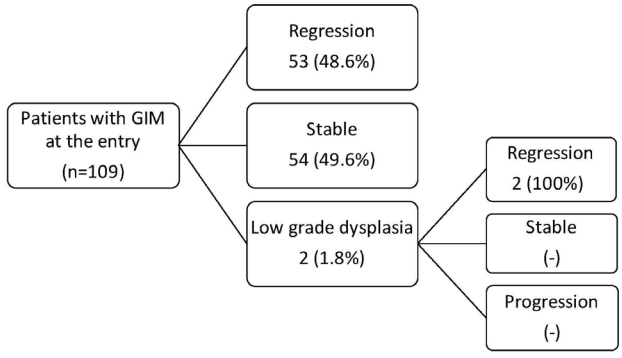

Figure 2. *Natural course of gastric intestinal metaplasia in Turkish patients*

GIM: Gastric intestinal metaplasia

http://doi.org/10.5472/marumj.1013580
Marmara Med J 2021;34(3): 229-233

Table II. *Details of 2 cases with detected low-grade dysplasia*

	Age	Gender	Initial Endoscopic Findings	Initial IM localization	Initial IM type /involvement	*H. Pylori* status	Time to progression(months)
Case-1	72	Male	Antral gastritis	Antrum	Incomplete/focal	(-)	54
Case-2	60	Female	Antral gastritis	Antrum+Corpus	Incomplete+Complete/ diffuse	(-)	129

H. pylori: Helicobacter pylori

4. DISCUSSION

The present study has demonstrated the general non-progressive disease course of GIM in the majority of patients during an average 3 years follow-up period. To the best of our knowledge, this is the first study to evaluate the natural course of GIMs in the Turkish population. In total, only two patients showed progression to LGD, but none of them progressed to HGD or invasive carcinoma. The progression rate was comparable with a recent large European multicenter prospective cohort study conducted in low incidence regions [15]. Out of 279 patients with GIM, only 4 (1.4%) progressed to HGD or gastric cancer. The neoplastic progression ratio was 0.3% in that study which may be accepted as comparable considering the longer follow-up period of approximately 4.7 years and the larger size of their cohort. About two-thirds of their patients remained stable, while the remaining one-third were found to be regressed in the follow-up. In our study, nearly half of our patients remained stable, and the remaining half showed no signs of GIM in the follow-up endoscopy.

The lower rate of regressed GIM patients detected in our cohort may be caused by the unmeasurable pseudo-regression rates mainly due to sampling and histological examination differences. One other contributor to this issue may be the success of *H. pylori* eradication, which decreased the initial rate of 26% to a final rate of 8%. Another interesting finding of our study is that the rate of diffuse involvement pattern of GIM decreased from 34% to 25% throughout the study, in line with the reduction in *H. pylori* rates. Therewithal, an increase in the number of GIMs limited to antrum from 39.4% to 51.8% was also observed, which may be related to the decrease in *H. pylori* and the diffuse involvement pattern. In 2018, the reversibility of GIM and its association with *H. pylori* eradication has been shown in a large Korean cohort [16]. Out of 598 prospectively enrolled patients, significant improvement of GIM was only shown in the *H. pylori* eradicated group compared to *H. pylori*-negative and *H. pylori* non-eradicated group. Still, our observational findings require validation and explanation with further prospective studies with a larger number of patients and translational investigations.

Gastric cancer screening is recommended to a subset of GIMs and the intensity of the surveillance program is decided based on the criteria such as extension, complete/incomplete subtype, etc. Patients with extensive GIM both in the antrum and corpus are recommended to undergo gastric cancer screening every 3 years, while a stricter surveillance program is only recommended to those with a family history of gastric cancer or advanced stages of atrophic gastritis [13]. The majority of our patients underwent a screening endoscopy within 1 or 2 years, but none exceeded 3 years as recommended. Besides, we offered screening endoscopy to all patients with GIMs in our center and did not apply a selection criterion to enter the surveillance program. In our initial cohort, 39.4% would not have been candidates for gastric cancer surveillance according to the aforementioned guideline recommendations, as they were restricted to antrum only. The lack of selection criteria implementation at the entry may be another explanation for the very benign behavior of GIMs in our study. For instance, a retrospective study conducted in Thailand with 91 GIM patients and followed-up for 5 years, showed that none of the GIMs with complete subtype has progressed, whereas a progression rate of 50% was detected in incomplete GIM subtype [17]. In our cohort, 24% did not show the characteristics of the more aggressive incomplete subtype and had complete GIM at the entry.

There are several limitations to our study. First, this was a retrospective observational study conducted in a single tertiary center. The biopsy taking in our center was implemented by experienced endoscopists and generally in line with the Sydney protocol [18] throughout the study, and all specimens were evaluated by an experienced gastrointestinal pathologist. Nevertheless, the retrospective nature of the study prevented us from homogenizing the biopsy taking and histological evaluation process. Besides, not all screening endoscopies were implemented within the same intervals, but none has exceeded the 3-year time interval suggested by the MAPS-II guideline.

In conclusion, although, considered as a preneoplastic lesion and offered surveillance globally, progression to dysplasia or invasive carcinoma was very low in a large unselected Turkish GIM cohort. Further prospective studies in larger cohorts are required to enlighten the obscure strategies in the surveillance of gastric malignancy.

Compliance with Ethical Standards

Ethical Approval: The study followed the tenets of the Helsinki Declaration and it was approved by the local Ethics Committee (Protocol No: 09.2019.808) of Marmara University, School of

http://doi.org/10.5472/marumj.1013580
Marmara Med J 2021;34(3): 229-233

Medicine. Owing to the retrospective nature of the study, the need for informed consent was waived.

Financial Support: No special funding was obtained.

Conflict of Interest Statement: There is no conflict of interest.

Authors' Contributions: C.O.D. : Drafting of the work. C.O.D., F.G. : Concept and design of the study. M.K., M.Y., M.Z.S., M.T.S., C.A.C. : Data acquisition. C.O.D. : Statistical analysis. C.A.C.: Reviewing pathologic specimens and interpretation of the results. All authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

REFERENCES

[1] Huang RJ, Choi AY, Truong CD, Yeh MM, Hwang JH. Diagnosis and management of gastric intestinal metaplasia: current status and future directions. Gut Liver 2019;13:596-603. doi: 10.5009/gnl19181.

[2] Graham DY. Helicobacter pylori update: gastric cancer, reliable therapy, and possible benefits. Gastroenterology 2015;148:719-31 e3. doi: 10.1053/j.gastro.2015.01.040.

[3] Zhu H, Xu H. Demographic and lifestyle risk factors for gastric intestinal metaplasia among US veterans. Am J Gastroenterol 2020;115:381-7. doi: 10.14309/ajg.0000000000000498.

[4] Oh S, Kim N, Yoon H, et al. Risk factors of atrophic gastritis and intestinal metaplasia in first-degree relatives of gastric cancer patients compared with age-sex matched controls. J Cancer Prev 2013;18:149-60. doi: 10.15430/jcp.2013.18.2.149.

[5] Trieu JA, Bilal M, Saraireh H, Wang AY. Update on the diagnosis and management of gastric intestinal metaplasia in the USA. Dig Dis Sci 2019;64:1079-88. doi: 10.1007/s10620-019-05526-5.

[6] Yee YK, Wong KW, Hui CK, et al. Prevalence and time trend of intestinal metaplasia in Hong Kong. J Gastroenterol Hepatol 2009;24:896-9. doi: 10.1111/j.1440-1746.2009.05799.x.

[7] Wong BC, Lam SK, Wong WM, et al. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 2004;291:187-94. doi: 10.1001/jama.291.2.187.

[8] Olmez S, Aslan M, Erten R, Sayar S, Bayram I. The Prevalence of gastric intestinal metaplasia and distribution of helicobacter pylori infection, atrophy, dysplasia, and cancer in its subtypes. Gastroenterol Res Pract 2015;2015:434039. doi: 10.1155/2015/434039.

[9] Choi AY, Strate LL, Fix MC, et al. Association of gastric intestinal metaplasia and East Asian ethnicity with the risk of gastric adenocarcinoma in a U.S. population. Gastrointest Endosc 2018;87:1023-8. doi: 10.1016/j.gie.2017.11.010.

[10] Song H, Ekheden IG, Zheng Z, Ericsson J, Nyren O, Ye W. Incidence of gastric cancer among patients with gastric precancerous lesions: observational cohort study in a low risk Western population. BMJ 2015;351:h3867. doi: 10.1136/bmj.h3867.

[11] Liu KS, Wong IO, Leung WK. Helicobacter pylori associated gastric intestinal metaplasia: Treatment and surveillance. World J Gastroenterol 2016;22:1311-20. doi: 10.3748/wjg.v22.i3.1311.

[12] Park YH, Kim N. Review of atrophic gastritis and intestinal metaplasia as a premalignant lesion of gastric cancer. J Cancer Prev 2015;20:25-40. doi: 10.15430/JCP.2015.20.1.25.

[13] Pimentel-Nunes P, Libanio D, Marcos-Pinto R, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy 2019;51:365-88. doi: 10.1055/a-0859-1883.

[14] den Hoed CM, Holster IL, Capelle LG, et al. Follow-up of premalignant lesions in patients at risk for progression to gastric cancer. Endoscopy 2013;45:249-56. doi: 10.1055/s-0032-1326379.

[15] den Hollander WJ, Holster IL, den Hoed CM, et al. Surveillance of premalignant gastric lesions: a multicentre prospective cohort study from low incidence regions. Gut 2019;68:585-93. doi: 10.1136/gutjnl-2017-314498.

[16] Hwang YJ, Kim N, Lee HS, et al. Reversibility of atrophic gastritis and intestinal metaplasia after Helicobacter pylori eradication - a prospective study for up to 10 years. Aliment Pharmacol Ther 2018;47:380-90. doi: 10.1111/apt.14424.

[17] Pittayanon R, Rerknimitr R, Klaikaew N, et al. The risk of gastric cancer in patients with gastric intestinal metaplasia in 5-year follow-up. Aliment Pharmacol Ther 2017;46:40-5. doi: 10.1111/apt.14082.

[18] Xirouchakis E, Laoudi F, Tsartsali L, Spiliadi C, Georgopoulos SD. Screening for gastric premalignant lesions with narrow band imaging, white light and updated Sydney protocol or both? Dig Dis Sci 2013;58:1084-90. doi: 10.1007/s10620-012-2431-x.