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Gastrıc Intestınal Metaplasıa and Covıd 19 Infectıon

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ABSTRACT

Gastric intestinal metaplasia (GIM) is defined as immigration of enteric or colonic mucosa within gastric lining.Gastric intestinal metaplasia (GIM) is a premalign condition seen in gastric lining. It is prevalent in Asia and may lead to gastric carcinoma at a rate of 1% annually. COVID 19, which has been a global issue since late 2019, causes mostly respiratory symptoms; however, some patients may present with gastrointestinal symptoms including diarrhea, vomiting (5%) and abdominal pain (3.8%).We tried in this text to handle any possible association between COVID 19 infection and GIM.

In this retrospective study we included 39 COVID 19 patients and 180 age-matched control subjects to compare rate of intestinal metaplasia. All statistical analyses were performed with SAS software (SAS Institute, Cary, N.C.). The clinical and radiological characteristics of patients were compared using Student's t-test.

Intestinal metaplasia was found in 11 (28%) of 39 patients while in 7 (3,9%) of 181 controls, which meant a statistical significance ($p<0,05$). Of the 181 subjects, atrophy was found in 39 (21%) whereas it was noted in 9 (23%) of 39 patients, which yielded no statistical significance ($p>0,05$).

We found that GIM is a premalignant condition that can lead to COVID 19 infection.

Key Words: COVID19, Intestinal metaplasia, Atrophy

Introduction

Gastric intestinal metaplasia (GIM) is defined as immigration of enteric or colonic mucosa within gastric lining. It is prevalent in Asia and may lead to gastric carcinoma at a rate of 1% annually (1). Atrophic gastritis and GIM have both been implicated in gastric carcinogenesis and should be followed by endoscopic screening programmes (2). Conditions potentially associated with GIM include H. pylori infection, older age, smoking, spicy foods, occupational status and presence of Interleukin 10-592 C/A (3).

COVID 19, which has been a global issue since late 2019, causes mostly respiratory symptoms; however, some patients may present with gastrointestinal symptoms including diarrhea, vomiting (5%) and abdominal pain (3.8%) (4). On the other hand, in a recent study involving 73 patients with COVID 19 infection revealed that half of patients tested positive in their stool samples (5). In this context, gastrointestinal involvement may be a key factor in disease initiation. However, there exists no work handling a potential association between COVID 19 infection and gastric premalignant conditions to date.

Materials and Materials

Between March and May 2020, we enrolled 39 patients with COVID 19 infection. (18 males and 21 females, with mean age being 58.5 ± 15 years). Data were collected from hospital records. Diagnosis of COVID infection was done based on PCR testing, compatible chest CT findings plus appropriate clinical picture. An age-matched control group (180 subjects; 90 females and males each, with mean age being 54.6±13.5 years) was selected from dyspeptic subjects without GIM. They were assessed for additional laboratory parameters obtained from hospital database. Those with severe underlying disease, including gastric cancer and gastric resection were excluded. Gastroscopy with antral biopsy had been performed in all patients two years before pandemic began. All study subjects' histopathological records obtained by gastroscopic biopsy were evaluated and compared.

Endoscopy and Histologic Examination: All endoscopic examinations were performed under

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Table 1. Characteristics of patient and control groups

	Group	Mean	Median	Standard Dev.	Min	Max.	p
Age	control	61,06	59,50	13,73	46,00	90,00	,063
	patient	62,15	64,00	16,74	27,00	96,00	
Hemoglobin	control	13,11	13,30	2,12	6,90	17,70	,090
	patient	12,48	12,70	2,05	7,30	16,30	
HTC	control	40,56	40,60	5,62	22,30	53,80	,065
	patient	38,65	40,70	6,72	15,70	49,40	
MCV	control	85,46	86,70	6,36	65,00	97,40	,024
	patient	88,13	88,60	7,78	50,00	99,00	
WBC	control	7,85	7,37	2,47	2,44	21,43	,292
	patient	9,40	7,59	9,02	3,10	60,22	
Neutrophil	control	4,69	4,17	2,20	1,07	19,29	,144
	patient	6,75	4,43	8,56	2,14	54,34	
Platelet	control	279,03	259,00	197,40	60,00	2696,00	,707
	patient	291,31	259,00	106,15	163,00	595,00	
Glycose	control	112,21	99,50	41,10	53,00	306,00	,133
	patient	128,60	107,00	60,56	83,00	409,00	
Urea	control	31,19	29,00	13,14	14,00	129,00	,063
	patient	39,21	31,00	25,16	14,00	134,00	
Creatinine	control	,80	,76	,27	,14	2,83	,228
	patient	,97	,81	,86	,34	5,72	
AST	control	23,74	20,00	17,99	10,00	220,00	,066
	patient	33,97	20,00	32,37	7,00	149,00	
ALT	control	23,64	18,00	21,42	7,00	161,00	,092
	patient	31,79	21,00	27,42	11,00	137,00	
Albumin	control	4,56	4,70	,53	3,20	5,50	,001
	patient	3,90	4,10	,86	2,14	5,10	
Ferritin	control	52,34	32,53	42,98	6,45	180,10	,011
	patient	407,67	164,70	626,09	6,60	2496,00	
TSH	control	2,02	1,57	1,92	,04	16,71	,302
	patient	3,11	1,77	5,02	,18	25,09	

propofol anesthesia using Fujinon videoscope (Tokyo, Japan). Biopsy samples were reviewed by a pathologist regarding GIM and H. Pylori status after being fixed in formalin using Giemsa and hematoxylin & eosin stainings, respectively. Intestinal metaplasia was classified as absent or present.

Statistical Analysis: All statistical analyses were performed with SAS software (SAS Institute, Cary, N.C.). The clinical and radiological characteristics of patients were compared using Student's t-test. Statistical significance was defined as a P value of less than 0.05.

Results

The characteristics of groups at baseline were well matched with respect to age and gender (Table 1, all P>0.05).

Data of 39 patients and 181 subjects were analyzed. Albumin and ferritin levels were found significantly lower and higher in patient group, respectively (p<0,05). MCV was higher in patient group (p<0,05). Intestinal metaplasia was found in 11 (28%) of 39 patients while in 7 (3,9%) of 181 controls (Table 2, p<0,05). Of the 181 subjects, atrophy was found in 39 (21%) whereas it was noted in 9 (23%) of 39 patients, which yielded no statistical significance (p>0,05).

Discussion

We found a clear association between acute COVID 19 infection and GIM in this work.

Diagnosing gastric disorders in the setting of acute COVID 19 infection is challenging due to risk of spreading during endoscopic procedure. Thus, we

Table 2. Rate of Gastric Intestinal Metaplasia within Groups

			GIM		
			0	1	Total
Group	Control	Count	174	7	181
		% within group	96,1%	3,9%	100,0%
		% within GIM	86,1%	38,9%	82,3%
		% of Total	79,1%	3,2%	82,3%
	Patient	Count	28	11	39
		% within group	71,8%	28,2%	100,0%
		% within GIM	13,9%	61,1%	17,7%
		% of Total	12,7%	5,0%	17,7%
Total		Count	202	18	220
		% within group	91,8%	8,2%	100,0%
		% within GIM	100,0%	100,0%	100,0%
		% of Total	91,8%	8,2%	100,0%

performed a retrospective study to detect gastric diseases.

A large Eestern study involving 78,985 patients revealed that prevalence of GIM in gastric biopsy specimens was 7% (6).

In this study, GIM was found significantly high in COVID 19 patient group.

A Polish multicenter study involving 1290 outpatients showed that risk of intestinal metaplasia within antrum depended greatly on presence of gastric peptic ulcer (OR = 3.85; 95% CI:2.35-6.32), age (OR = 1.05; 95% CI:1.04-1.07), being active or ex-smoker (OR = 1.42; 95% CI:1.10-1.84), alcohol (OR = 1.32, 95% CI:1.01-1.75) and chronic antral gastritis (OR = 1.31; 95% CI:1.00-1.70) (7).

While bacterial virulence genes of H. pylori including cagA and vacA m1 are strongly linked to atrophic gastritis, environmental and host factors are crucial for IM rather than H. pylori infection alone (3).

The development potential of gastric cancer depend on various variables including advanced age, male sex, smoking status and family history. Older age and male gender yields a 5- and 2-fold increased risk, respectively (8).

As currently described in Chinese report, elderly men were mostly affected by COVID 19 infection and mortality rates were also higher in men compared to women (9).

Differences in prevalence of GIM between Eastern and Western countries has largely been attributed to variations in traditional food culture practices. It was described that GIM were more prevalent in Asian countries than Western world due to higher prevalence of H.pylori, low socioeconomical status and consumption of dairy products (10).

The link between COVID 19 infection and GIM may be related to multiple factors including a genetic predisposition, viral damage mechanism targeting intestinal system and unique susceptibility of the gastrointestinal system to environmental agents including raw foods and bat meat, which have been postulated as trigger for developing COVID 19 infection in Wuhan city.

On the other hand, the major clinical symptoms of COVID-19 patients included fever, cough and fatigue; while a certain proportion of patients presented with gastrointestinal symptoms (11).

A recent cohort involving 140 patients with COVID-19 from Wuhan, China showed that gastrointestinal symptoms were described in nearly 40% of the patients; as nausea in 24 (17.3%), diarrhea in 18 (12.9%), and vomiting in 7 (5.0%) (12).

In addition, it was shown that the SARS-CoV RNA was detected in stool samples of SARS patients (13).

ACE2 plays a crucial role in cellular entry for SARS-CoV-2, which means that ACE2-positive cells may act as target cells and are susceptible to infection (14).

Recent bioinformatics analysis on available single-cell transcriptomes data of normal human lung and gastrointestinal system was carried out to identify the ACE2-expressing cell composition and proportion, and revealed that ACE2 was not only highly expressed in the lung AT2 cells, but also in esophageal epithelial cells plus absorptive enterocytes in ileum and colon (15).

Single-cell RNA-Seq results showed that ACE2-positive-cell ratio in digestive tract organs was significantly higher than that in lung. Mei Chu et al. showed in their study that ACE2 expression was

higher in digestive system than lung and in tumor tissue than normal one (16).

Recent single cell RNA sequencing data from 2 independent cohorts revealed a significant enrichment of ACE2 expression in cholangiocytes (59.7% of cells) than hepatocytes (2.6% of cells), suggesting that COVID-19 might lead to direct damage to the intrahepatic bile ducts (17).

Furthermore, electron microscopy on biopsy and autopsy specimens showed active viral replications in both small and large intestines (18). Daniel et at. found that famotidin decreased rate of death and need for intubation in hospitalized patients (19).

In this context, both GIM and COVID 19 infection could share same underlying etiologies and GIM may be a harbour for virus at gastrointestinal tractus. Focus on GIM prevention may block an enterance point of COVID 19 infection. The data above suggests that GIM affects gastric mucosal tissue with formation of toxic products, which may play a potential pathogenic role in developing COVID 19 infection.

There are several important limitations of the study. First, our study was retrospective. Second, we could not obtain full medical history among study population. Third, we did not assess comorbid illnesses through clinical evalauation. Lastly, we did not obtain dietary behaviours of the subjects with GIM which may play a role in that disease course.

On the other hand, the current study is the first to assess impact of GIM on COVID 19 infection. We postulate that GIM is a premalignant condition that can lead to COVID 19 infection. Further studies are required to determine whether GIM can induce COVID 19 infection.

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