The impact of *H. pylori* and/or *T. gondii* infection on recurrence of gastritis and gastric ulcer

Original Article

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ABSTRACT

Background: Concomitant *H. pylori* and *T. gondii* infections are two widespread diseases transmitted by fecal-oral route. Several studies documented association of both infections in gastritis and peptic ulcer diseases.

Objective: The aim of this work is to evaluate the relation between recurrent gastritis or gastric ulcers and coinfection with *H. pylori* and *T. gondii*.

Subjects and Methods: Investigations included upper gastrointestinal tract (GIT) endoscopic biopsy, detailed personal questionnaire, serum detection of anti-cag A and anti-vac A for *H. pylori*, anti-*Toxoplasma* IgM and IgG antibodies. Selected cases were from patients attending the Gastroenterology and Hepatology Department of Kafrelsheikh University Hospital. In total, 80 participants were distributed as 32 naïve cases, 28 recurrent and 20 with no gastric infections as control. For diagnosis of *H. pylori*, sandwich ELISA immunoassay (EIA) test was performed to detect *H. pylori* surface coproantigen in fresh stools taken after endoscopy. In patients' serum samples, IgG for *H. pylori* cag-A and vac-A antigens, IgM and IgG for *T. gondii* were detected by ELISA.

Results: Recurrence of *H. pylori* infection increased in age groups 21-30 and 31-40 years, mainly in males and in those eating junk foods. Severe gastric ulcers appeared in combined *H. pylori* and *T. gondii* infections. Recurrent cases showed 71.4% positive *H. pylori* anti-cag A, 57.1% *H. pylori* anti-vac A, 35.7% both *H. pylori* antigens, 57.1% anti-*Toxoplasma* IgM, and 71.4% anti-*Toxoplasma* IgG, 35.7% concomitant bacterial and parasitic infection. High IgM positivity rate was recorded in recurrent cases while IgG was recorded in naïve cases.

Conclusion: Toxoplasmosis when combined with *H. pylori* participates in recurrence of the latter, causing higher severity of gastritis and gastric ulcer. Eating junk foods and being middle aged are contributing risk factors.

Keywords: coproantigens; gastritis; gastric ulcers; *H. pylori*; *T. gondii*; recurrence.

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INTRODUCTION

The association of the two widespread infectious diseases caused by the gram negative bacterium, *H. pylori*, and the apicomplexan parasite, *T. gondii*, was studied in gastritis and peptic-ulcer formation[1]. This positive association may occur by the fecal-oral route from cat feces. High detection rates of *H. pylori* in cat feces raised the possibility of zoonotic transmission of both pathogens[2].

Treatment of *H. pylori* infection markedly decreases the occurrence of peptic ulcers. It was found that gastric ulcers tend to recur more than duodenal ulcers usually at the same original site[3]. The most common complication associated with peptic ulcer disease is peptic ulcer bleeding. Thus understanding the role of *H. pylori* in the pathogenesis of this bleeding is crucial to prevent upper GIT hemorrhage[4]. Of note, 30% of *H. pylori* infected patients present by mild to severe upper GIT diseases such as gastritis, peptic ulcer, gastric cancer or mucosa-associated lymphoma in spite of having been infected during childhood or being asymptomatic for a long period[5].

Combination of *H. pylori* infection with *A. lumbercoides* and *T. gondii* altered *H. pylori* gastritis in rodents' models. Elevation of IgE and anti-inflammatory Th2-IgG1 responses to *H. pylori* was found to correlate with *A. lumbercoides* IgG antibodies detection. Reduction of Th1-IgG2, IgG3 and IgG4 responses to *H. pylori* correlated with high *T. gondii* titres[6].

Possession of a well-known virulence factor as the cytotoxin-associated gene A (cag-A), allows some *H. pylori* strains to cause more severe inflammation and widespread atrophy in gastric mucosa than those lacking this gene[7,8]. Early immunological detection of cag-A protein just after *H. pylori* infection

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by determination of specific gastric mucosal IgA and serum IgG antibodies marks the cag-A-positive strains as the pathogenic and immune dominant agent in cases of gastric ulcers[9]. A significant association of vac-A genotypes *m1, s1m1* and *s2m1*, as virulence factors for peptic ulcer, was observed in *H. pylori* infected patients[10].

On the other hand, bidirectional endoscopy in an immunocompromised patient with disseminated toxoplasmosis, revealed large ulcerations in the gastric cardia and fundus with severe active gastritis and ischemic changes[11]. This was attributed to a strong immune response controlled by a series of regulatory mechanisms against *Toxoplasma*. The disturbed balance between CD4 and CD8 cells, and the immunosuppression mediated by HLA-DR molecules is enhanced, which may lead to gastritis and diarrhoea[12].

Manifestations of chronic infections with *T. gondii* and/or *Helicobacter* spp. probably depend on the host immune response and patients who suffer from chronicity were found to carry more than one pathogen[13]. Although the investigators were unable to explain how multiple active infections interact with each other or how they affect the disease prognosis, they claimed that concomitant infection by *T. gondii* and *H. felis* was found to enhance the susceptibility of mice to *H. felis* infection[13].

This was associated with significant elevation of gastric mucosal IFN-γ and IL-12, considerable reduction of IL-10, severe gastric mucosal inflammation, loss of parietal cells, atrophy, and metastatic cell changes. Consequently, the aim of the present work was to evaluate the relation between recurrent gastritis and/or gastric ulcers and coinfection with *H. pylori* and *T. gondii*.

SUBJECTS AND METHODS

This case-control study was conducted during the period from January 2020 to July 2020. Stool and serum samples were obtained from patients in the Gastroenterology and Hepatology Departments, Kafrelsheikh University Hospital. Samples were transferred to Parasitology and Microbiology Departments, Faculty of Medicine, Kafrelsheikh University for parasitological and microbiological investigations.

Study design: Patients complaining of sever upper GIT symptoms were regarded as eligible for endoscopy, and stool analysis for *H. pylori* coproantigens. Those with normal endoscopic findings and negative for *H. pylori* coproantigens were considered as apparently healthy controls. Patients with endoscopic findings and positive for *H. pylori* coproantigens who presented for the first time were considered as naïve cases; and those who returned after one year because of persistent symptoms were considered as recurrent cases. All cases were subjected to *H. pylori* and *T. gondii* analysis by sandwich ELISA immunoassay (EIA) for coproantigen detection in stool specimens and by ELISA for serum antibodies against *H. pylori* and *T. gondii*.

Participants: History was recorded from patients including their type of diet. Patients (no.= 60) found eligible for upper GIT endoscopy came to the hospital complaining of epigastric pain, heartburn, abdominal discomfort and/or vomiting, not improved by empirical anti-acids or proton pump inhibitors alone. The inclusion criteria included naïve *H. pylori* infected patients (no.=32) having upper GIT symptoms for the first time and confirmed diseased by endoscopy. Recurrent *H. pylori* patients (no.=28) were those complaining of the same symptoms within one year. Choice of apparently healthy controls (no.= 20) depended on the endoscopic examination (pink, smooth and lustrous gastric mucosa). The exclusion criteria included patients who had taken anti *H. pylori* therapy four weeks before endoscopy, or had any gastro-intestinal, hepatic, or renal diseases. Fresh stool and serum samples were collected from each participant after endoscopy.

***H. pylori* surface coproantigen (*Hp*SA) test:** A fresh stool sample from each participant was collected and stored at -20^{0}C until analysis. Detection of *Hp*SA in stools was by EIA for antigen detection according to the manufacturers' instructions[14] (Premier Platinum HpSA, Meridian Bioscience Inc, USA).

Antibody assay against *H. pylori* coproantigens: Serum samples were screened for *H. pylori* antibodies (anti-cag-A IgG, and anti-vac-A IgG) by ELISA[15] (Xingkang Company, Shenzhen, China). The cut off values were determined for both. The results were interpreted by the positions of the matrices and the mean grey levels of the spots in the matrices.

Detection of anti-*Toxoplasma* IgM and IgG in patients' sera: Serum samples were screened using ready-made ELISA kits (Abcam, USA), and an ELISA plate reader (Bio-Rad, Hercules, CA). The optical density was measured at 450 nm and the antibody (IgM and IgG) titre for each sample was calculated[16]. Following the manufacture's protocol, a *Toxoplasma* IgM titre <0.8 was considered negative; 0.8–1.0 was considered equivocal; and > 1 was considered positive. A *Toxoplasma* IgG titre <5 was considered negative; 5-7 was equivocal and >7 was positive.

Study groups: According to the results of stool and serum investigations, as well as endoscopy, patients were categorized into 8 groups as shown in the following table.

Groups (No. of cases)	Groups identity	Characteristics
1 (4)	**Infected, sero-negative group**	Patients positive for *H. pylori* antigen in stools and serologically negative in all serum samples.
2 (4)	***H. pylori*, cag-A group**	Patients positive for anti-cag-A IgG antibodies only.
3 (2)	***H. pylori*, vac-A group**	Patients positive for anti-vac-A IgG antibodies only.
4 (2)	**Both *H. pylori* antigens group**	Patients positive for both anti-cag-A and anti-vac-A IgG antibodies.
5 (4)	**Recently acquired toxoplasmosis group**	Patients positive for anti-*Toxoplasma* IgM antibodies only.
6 (6)	**Chronic (latent) toxoplasmosis group**	Patients positive for anti-*Toxoplasma* IgG antibodies only.
7 (38)	**Concomitant infections group**	Patients positive for concomitant anti-cag-A, anti-vac-A, anti-*Toxoplasma* IgM, or anti-*Toxoplasma* IgG antibodies.
8 (20)	**Controls**	Patients having symptoms, with healthy endoscopic gastric mucosa, negative *H. pylori* coproantigens, and positive *Toxoplasma* IgG only.

Ethical approval: The study was approval by Ethical Committee of Faculty of Medicine, Kafrelsheikh University, 2019. We followed the guidelines as per the Declaration of Helsinki for involving human participants. Permissions in the form of informed consents were taken from the participants. All patients and control subjects were informed of the investigations results.

Statistical analysis: Data were tabulated and analysed using SPSS version 23. Demographic data were presented as categorical groups, and serological tests titres were presented as mean ± standard deviation. Data for categorical variables was expressed as percentages. Differences between variables were compared by using chi-square analysis (X^2). Fisher exact test was used if the expected count was less than 5. *P* value <0.05 was considered as statistically significant relationship between variables.

RESULTS

Recurrence of gastric ulcer: In the 28 cases with recurrent gastritis the highest prevalence was in the age groups 21-30 years and 31-40 years with the same percentage (42.9%). In the 32 naïve cases, the prevalence was in the 21-30 years age group (37.5%). Both were statistically significant (P<0.05). Regarding the gender, recurrence in males (71.4%) was significantly (P<0.05) more than in females (28.6%). In both recurred and naïve cases distribution by diet habits showed insignificant prevalence in junk foods compared to home and fat diets (Table 1).

Correlation of gastritis severity and the type of infection: Endoscopic examination categorized fundus findings as mild, moderate, and severe gastritis. Severe gastritis (erosions and ulcers) ranged from erosive fundal gastritis to severe pan gastric congested mucosa with hemorrhagic fundal gastritis (Figure 1d).

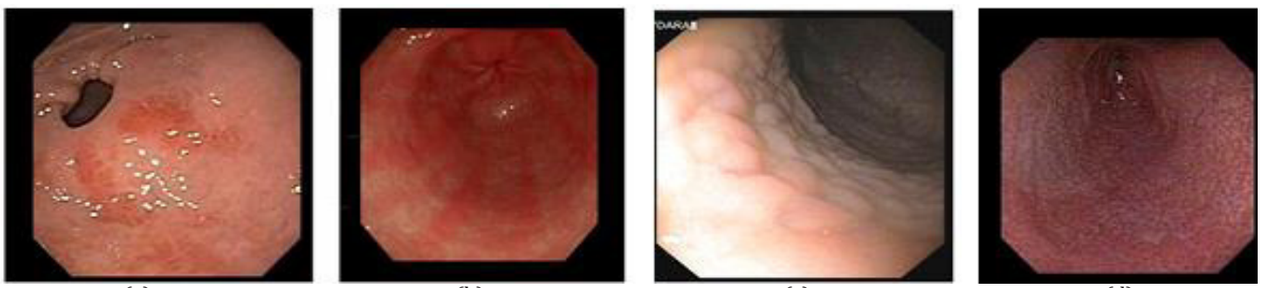
Table 1. Patients complaining of naïve and recurrent gastric problems in relation to age, sex and diet.

	Control (n=20)	Naïve cases (n=32)	Recurrent cases (n=28)	Statistical analysis	
	No. (%)	No. (%)	No. (%)	X^2	*P* value
Age					
11-20	6 (30.0)	6 (18.8)	0 (0.0)		
21-30	7 (35.0)	12 (37.5)	12 (42.9)	**14.36@**	**<0.05***
31-40	5 (25.0)	6 (18.8)	12 (42.9)		
41-50	2 (10.0)	6 (18.8)	4 (14.3)		
51-60	0 (0.0)	2 (6.3)	0 (0.0)		
Sex					
Male	11 (55.0)	20 (62.5)	20 (71.4)	1.339	>0.05
Female	9 (45.0)	12 (37.5)	8 (28.6)		
Diet					
Home	13 (65.0)	16 (50.0)	8 (28.6)	8.53	<0.05*
Junk	5 (25.0)	12 (37.5)	18 (64.3)		
Increased fats diet	2 (10.0)	4 (12.5)	2 (7.1)		

@: Fisher's exact was done for age tables as 60% of cells having an expected count < 5. ***:** Significant (P <0.05).

Severity of endoscopic findings in G7 associated with concomitant infection by *H. pylori* and *T. gondii* was in 18/60 (30%) of all patients and in 18/18 (100%) of severe cases. Moderate gastritis observed as moderate antral gastritis, moderate fundal gastritis, granular mucosa of the body or congested erythematous body with longitudinal erosions (Fig. 1b and c), appeared to be higher in concomitant infections 12/16 (75%). Mild gastritis that ranged from mild antral erythematous mottling to antral gastritis with duodeno-gastric biliary reflux (Figure 1a) occurred in 8/26 (30.8%) of concomitant infections (G7), and in 6/26 (23.1%) of chronic latent toxoplasmosis (G6). Total moderate and mild cases of gastritis represented 16/60 (26.7) and 26/60 (43.3%) of all patients respectively. Relation between all variables was statistically significant (P < 0.001), (Table 2).

The impact of *H. pylori* and *T. gondii* infections in naïve and recurrent gastric problems: All naïve and recurrent cases showed positive stool samples for *H. pylori* coproantigen. The seroprevalence of *H. pylori* virulence factors, anti-cag-A and anti-vac-A IgG antibodies, was significantly positive (P<0.001) in recurrent cases (71.4% and 57.1% respectively) being higher than in positive naïve cases (25% and 43.7% respectively) (P<0.001) (Table 3). Regarding toxoplasmosis, the *Toxoplasma* IgM test was significantly positive (P<0.001) in naïve and recurrent cases by 12.5% and 57.1%, respectively. *Toxoplasma* IgG test was significantly positive (P<0.05) in naïve and recurrent cases by 81.3% and 71.4% respectively (Table 3).



(a) (b) (c) (d)

Fig. 1. Endoscopic findings of different degrees of gastritis severity in patients with *H. pylori* infections and/or toxoplasmosis. **(a)** Patchy antral gastritis, erythematous mottling. **(b)** Moderate antrum gastritis, erythematous mottling. **(c)** Granular mucosa (body). **(d)** Pan-gastritis, erythematous mottling.

Table 2. Severity of gastritis in the different groups.

Groups	Severity of gastritis (Endoscopy)				Statistical analysis	
	Mild No. (%)	Moderate No. (%)	Severe No. (%)	Total	Fisher exact test	*P* value
1	4 (15.4)	0 (0)	0 (0)	4 (6.7)		
2	2 (7.7)	2 (12.5)	0 (0)	4 (6.7)		
3	0 (0)	2 (12.5)	0 (0)	2 (3.3)		
4	2 (7.7)	0 (0)	0 (0)	2 (3.3)	**29.41**	
5	4 (15.4)	0 (0)	0 (0)	4 (6.7)	**<0.001**	
6	6 (23.1)	0 (0)	0 (0)	6 (10)		
7	8 (30.8)	12 (75)	18 (100)	38 (63.3)		
Total	26 (43.3)	16 (26.7)	18 (30.0)	60 (100)		

***:** Significant (P <0.05).

Table 3. *H. pylori* and *T. gondii* infections in cases with naïve and recurrent gastric problems.

Type of test	Test result	Control (n=20)	Naïve cases (n=32)	Recurrent cases (n=28)	Statistical analysis	
		No. (%)	No. (%)	No. (%)	X^2	*P* value
***H. pylori* cag-A**	**Positive**	0 (0.0)	8 (25.0)	20 (71.4)	28.51	< 0.001*
	Negative	20 (100.0)	24 (75.0)	8 (28.6)		
***H. pylori* vac-A**	**Positive**	0 (0.0)	14 (43.7)	16 (57.1)	17.14	< 0.001*
	Negative	20 (100.0)	18 (56.3)	12 (42.9)		
***Toxoplasma* IgM**	**Positive**	0 (0.0)	4 (12.5)	16 (57.1)	17.63	< 0.001*
	Negative	20 (100.0)	28 (87.5)	12 (42.9)		
***Toxoplasma* IgG**	**Positive**	6 (30.0)	26 (81.3)	20 (71.4)	11.02	< 0.05*
	Negative	14 (70.0)	6 (18.7)	8 (28.6)		

***:** Significant (P <0.05).

Relation between *H. pylori* positive cases and the presence of virulent factors, cag-A or vac-A antibodies: *H. pylori* infected cases with cag-A positive versus negative status were 28/60 (46.67%) and 32/60 (53.33%) respectively. On the other hand, *H. pylori* cases with vac-A positive versus negative status were 30/60 (50%) for each group of cases, showing statistical insignificance (*P*>0.05) (Table 4).

Relation of *Toxoplasma* antibody positivity in naïve and recurrent gastritis cases: The difference in IgM mean values in naïve (0.90+1.50) versus recurrent cases (2.89+2.34) was statistically significant (*P*<0.0001). The difference in IgG mean values which were on the whole positive in both naïve (30.68±17.43) and recurrent (14.60±9.65) cases was statistically insignificant (Table 5).

Table 4. *H. pylori* positive virulent factors cag-A and vac-A status.

		***H. pylori* cag-A**			**Statistical analysis**	
		Negative	**Positive**	**Total**	X^2	***P* value**
***H. pylori* vac-A**	**Negative**	14 (46.67%)	16 (53.33%)	30	1.07	> 0.05*
	Positive	18 (60%)	12 (40%)	30		
	Total	32 (53.33%)	28 (46.67%)	60		

***:** Insignificant.

Table 5. *Toxoplasma* mean IgG and IgM antibody values in naïve and recurrent gastric problems.

	Control (n=20)	**Naïve cases (n=16)**	**Recurrent cases (n=14)**	**Statistical analysis**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	***P* value**
***Toxoplasma* IgM**	0.39 ± 0.36	0.90 ± 1.50	2.89 ± 2.34	< 0.001*
***Toxoplasma* IgG**	6.78 ± 7.75	30.68 ± 17.34	14.60 ± 9.65	> 0.05

***Toxoplasma* IgM evaluation:** Negative: <0.8, Equivocal: 0.8-1; Positive: >1; ***Toxoplasma* IgG evaluation:** Negative: <5, Equivocal: 5-7 Positive: >7. ***:** Significant (*P* value <0.05).

DISCUSSION

Several virulence factors including those of *H. pylori* constitute high risks for severe gastritis. A recent study encouraged researchers to perform more multidisciplinary efforts to understand the virulence factors of gastric complications[17,]. Gale *et al*.[1] reported that *H. pylori* and latent toxoplasmosis positive individuals were more liable to cognitive deficiency because of gastritis and vitamin B12 deficiency. This encouraged us to investigate the outcome of these two infections on recurrent gastritis.

In our study evaluation of factors that may influence the recurrence of gastric ulcers revealed that the most affected age groups were 21-30 years and 31-41 years as compared to previously reported mean age of 58.2 years old, with occurrence of peptic ulcer in 29.6% of patients over 70 years of age[18]. In another report, benign gastric ulcer (BGU) recurrence after eradication of *H. pylori* was recorded at the mean age of 65.3±15.2 years, while in the non-recurrent group, the mean age was 49.1±10.9 years[19]. Additionally, we noted that recurrence among males was significantly higher (71.4%; P<0.05) than in females (28.6%) which is in accordance with the stated 70.3% of peptic ulcers in males[19].

According to Mahmood *et al*.[20], there was significant association between the increased prevalence of *H. pylori* infection and eating food from street vendors, while cases who denied that and preferred eating fruits, showed no associated infection. This agrees with our results concerning the highest percentage of recurrence (64.3%) among all recurrent cases who commonly eat junk foods. A similar report concerning individuals consuming junk food showed high prevalence of *H. pylori* infection with strong association to acid peptic disease in 157/200 males and 142/200 females[21]. Accordingly, it was recommended that lipids intake in diets, without concentration of saturated fats, should be adjusted to protect against peptic ulcers[22].

The current study revealed that in G7 patients concomitantly infected by both *H. pylori* and *T. gondii*, 100% suffered from severe gastritis with gastric erosions and ulcers; while 75% and 30.8% showed moderate and mild pathological signs respectively. The remaining mild gastritis cases (69.2%) suffered from a single infection by either *H. pylori* or *T. gondii*. In consensus, it was reported that *H. pylori* antigen in stools was positive in 79/86 of antral or corpus gastritis cases, 19/21 of duodenitis cases, 2/2 of gastric ulcer cases, 8/8 of duodenal ulcer cases, 1/1 of gastric and duodenal ulcer cases and 17/21 of esophagitis cases[23]. It appears that our report is the first record of the effect of toxoplasmosis on gastritis severity in humans. We recorded that in *H. pylori* negative cases, serum anti-*Toxoplasma* IgM was positive in 4/26 cases showing mild antral erythematous mottling (mild cases); and serum anti-*Toxoplasma* IgG was positive in 6/26 cases showing antral gastritis with duodeno-gastric biliary reflux (mild cases); while in concomitant infections there were 8/26 mild cases, 12/16 moderate cases and 18/18 severe cases of gastritis. In a recent case report of a patient complaining of odynophagia, dysphagia

and dyspepsia, toxoplasmosis was involved alone as a zoonotic infection. Clusters of tachyzoites were discovered in histopathological sections of esophageal ulcers containing gastric inflammatory lymphocyte and eosinophil infiltrates[24].

Another group of researches[25] recorded examination of a gastric biopsy report from a-22-years old AIDS patient showing *T. gondii* infection of the stomach which appeared as intracellular trophozoites harboring the necrotic gastric epithelium, macrophages and muscle cells, in addition to the presence of true cysts and psuedocysts.

Our evaluation of the clinical significance of cag-A and vac-A antibodies in severe gastritis with gastric ulcers, showed weak expression in relation to mild and moderate gastritis only. On the other hand, the expression of these two *H. pylori* proteins, was supposedly related to the bacterium pathogenicity[26]. The researchers acknowledged that cag-A cytotoxin is involved in the development of peptic ulcer and is common in gastric adenocarcinoma, and that some subtypes of vac-A cytotoxin are considered as risk factors. Of note, in our study recurrent gastritis and gastric ulcers cases the *H. pylori* cag-A and vac-A cytotoxins revealed high positivity (71.4% and 57.1%, respectively) proving their value as detectable markers for recurrence. Another study[18] had revealed *H. pylori* infection in 51.4% of recurrent cases. This was advocated by other studies[27-30].

Our study may be considered a new record for the role of anti-*Toxoplasma* IgM and IgG in naïve and recurrent cases of gastritis and gastric ulcers. Detection of IgM antibodies appeared more positive in recurrent cases being 57.1% versus 12.5% in naïve cases; while IgG antibodies were more positive in naïve cases being 81.3% versus 71.4% in recurrent cases. Therefore, both clinical conditions of naïve and recurring gastritis may be related to infection with *T. gondii*. It is interesting for us to note that in recurrent cases the mean anti-*Toxoplasma* IgM antibody was higher than in naïve cases, and vice versa the mean anti-*Toxoplasma* IgG in naïve cases was higher than in recurrent cases, indicating that the patients with gastric ulcer recurrence presented themselves earlier due to more acute symptoms, than those with chronic infections.

In conclusion, toxoplasmosis participates in recurrence of gastritis and gastric ulcers whether alone or in combination with *H. pylori*. Recurrence of gastric affection in toxoplasmosis patients is more common in acute infections. *H. pylori* cag-A is more frequent in recurrent cases. Recurrence is more obvious in the middle age, in males, and in those eating junk foods.

Author contributions: All authors participated in the study design. Elawamy WE, Ghazy AA and Taha AE shared in performing all investigations, results interpretation, data analysis and writing the manuscript. Haydara T and Ghazy AA collected clinical samples and literature data. Haydara T performed the upper GIT endoscopy for all patients. Elawamy WE contributed to editing of the manuscript for publication.

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