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Anti-*Saccharomyces cerevisiae* antibodies (ASCA) in peptic ulcer disease with *Helicobacter pylori*

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Abstract

Anti-Saccharomyces cerevisiae antibodies (ASCA) is related to the pathogenesis of Crohn's disease as digestive tract inflammation. But the relationship between ASCA and peptic ulcer as upper digestive tract inflammation is unknown. The aim of this study was to determine the prevalence of ASCA positivity in patients with peptic ulcer and the relationship between ASCA and *Helicobacter pylori*. Total 128 patients with peptic ulcer were enrolled at Nagoya university hospital from 1999 to 2005. Serum samples obtained from with all peptic ulcer patients were examined. Determination of ASCA was performed by ELISA method. All patients were confirmed *H. pylori* infection. 10 patients with *H. pylori* infection were treated with eradication therapy. Fifty-five patients of 128 were suffered from active peptic ulcer. Of 128, 38 patients were ASCA-positive. 34 patients of 38 ASCA positive patients were active ulcer and other 4 patients were ulcer-scar. ASCA positivity in active ulcer patients was more significant than that in ulcer-scar. The *H. pylori*–positive patients were 78. Thirty patients were ASCA positive in 78 *H. pylori* positive. Eight patients was ASCA positive in 50 *H. pylori* negative patients. ASCA in *H. pylori* positive was increasing more than that in *H. pylori* negative patients significantly. ASCA positivity was found to be correlated with eradication. All successful eradication patients were ASCA negative after treatment even if 3 patients were ASCA positive before eradication therapy. Our results show that ASCA is associated with both peptic ulcer and *H. pylori* infection.

Keywords: ASCA; Helicobacter pylori; Peptic ulcer; ELISA

1. Introduction

Helicobacter pylori (*H. pylori*) is a microaerophilic, Gram-negative spiral bacterium that is recognized as a pathogen [1]. *H. pylori* is associated with peptic ulcer and malignant lymphoma, and gastric cancer [2, 3]. Most gastric ulcers occur with chronic diffuse gastric inflammation [4]. Clinical and histological studies have suggested that *H. pylori*-related gastritis and gastric ulcer represent a continuum of progressive disease [5]. Among patients with gastric ulcers who were treated with three antibacterial drugs and ranitidine, the incidence of recurrent ulcers was significantly reduced after the eradication of *H. pylori* [6]. However, even if *H. pylori* exists in stomach, some patients do not suffer from peptic ulcer. This reason is unknown, and some factors may be associated with the occurrence of peptic ulcer.

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Saccharomyces cerevisiae (SC) is a ubiquitous yeast found in a variety of locations, including plants and underground [7]. Humans have used yeast to make many foods. In general, SC is not a pathogen. However, it has been suggested that various organs are affected and injured in SC mycosis under unhealthy condition [7].

Several reports show that *Anti-Saccharomyces cerevisiae* antibodies (ASCA) is related to the pathogenesis of Crohn's disease (CD) as digestive tract inflammation [8]. It is useful as a serological test for CD as a biomarker. ASCA directed against cell wall oligomannoside epitope have been proposed as a serological marker for CD [9]. The role of of ASCA's in CD is completely unknown, but one hypothesis links them to increased intestinal permeability. 50-60% of patients with CD exhibit an activity-related increase in intestinal permeability, and this increase might be predictive for relapse [10]. Increased exposure of the epithelium to common food antigens on the activity of stable CD disease caused the exacerbating of CD status [11]. These results suggest that dietary yeast may affect the activity of CD known as mainly lower digestive tract inflammation.

Peptic ulcers derived from *H. pylori* infection with inflammation of the upper gastrointestinal tract may also be associated with ASCA. However, the relationship between ASCA and peptic ulcer as upper digestive tract inflammation is unknown.

The aim of this study was to determine the prevalence of ASCA positivity in patients with peptic ulcer and the relationship between ASCA and *H. pylori*.

2. Material and methods

2.1. Patients

Two hundred thirty-two patients who had abdominal symptoms were enrolled at Nagoya University hospital and associated health care centers from 1999 to 2005.They were ruled out inflammation bowel disease. Informed consent was obtained from the patient and permission for the study was received from our institution. The status of peptic ulcer was confirmed endoscopically. By definition, superficial erosions were not considered to be ulcers. For determination of *H. pylori* status, biopsy study was performed during endoscopic procedure. Three biopsy specimens from antrum were taken for culture, rapid urease test, and histopathology. Two biopsy specimens from great curvature were obtained for culture and histopathology. For histopathological examination, formalin-fixed gastric biopsy specimens were stained with Gimsa stain and histopathologist examined the preparation. Culture of gastric biopsy specimens was performed on *H. pylori* selective agar palates at 37°C under microaerophilic conditions for 4 days. Gram-negative and oxidase, catalase, urease test– positive spiral, curved rods were identified as *H. pylori.* Urea breath test was also performed as a reconfirmation of *H. pylori* presence.

2.2. Eradication therapy

Ten peptic ulcer-patients with *H. pylori* infection were treated with eradication therapy.

In case of eradication therapy group, we assessed the status of peptic ulcer and *H. pylori* with endoscopy at one month after therapy. By endoscopic biopsy examination, the success of *H.pylori* eradication was evaluated by rapid urease test, histology, and culture examination. Patients received the eradication regimen comprising omeprazole 40mg od, clarithromycin 800mg (400 mg bd) and amoxicillin (500mg bd) for 7 days. Adequate compliance was defined as consumption of more than 90% of the scheduled drug and checked by staff at Nagoya University associated health care center through pill counting.

2.3. ASCA IgG and IgA assessment

Serum samples obtained from with all peptic ulcer patients were examined. Determination of ASCA was performed by ASCA IgA kit and ASCA IgG kit (Genesis Diagnosis Ltd. Little port, UK) according to the instruction manual. We defined ASCA positive status if either ASCA IgG or IgA is positive.

2.4. Statistics

Comparison of results was made by Fisher's exact test. $p<0.05$ was regarded as denoting statistical significance.

3. Results

All 232 patients were performed in this study and no patients were failed. Populations of patients were128 peptic ulcer patients (gastric ulcer (GU) 68, duodenal ulcer (DU) 60) and 104 non-peptic ulcer patients. Fifty-five patients of 128 were suffered from active peptic ulcer. Of 128, the numbers of open ulcer and scar ulcer were 55 (43%) and 73 (57%) , respectively. The numbers of GU and DU were 68 (53%) and 60 (47%), respectively (Table 1).

Table 1 Clinical characteristic of 128 peptic ulcer patients

	GU	**DU**	**Total**
Open	27	28	55
Scar	41	32	73
Total	68	60	128

Thirty-eight patients were ASCA-positive (29.6%) of 128 peptic ulcer patients. 34 patients of 38 ASCA positive patients (86.8%) were active ulcer (GU 11, DU 23) and other 4 patients (13.2%) were ulcer-scar (GU 2, DU 2). ASCA positivity rate in active ulcer patients was more significant than that in ulcer-scar (p<0.05). The prevalence of ASCA positivity in DU was greater than that in GU (p<0.05) (Table 2).

Table 2 Characteristic of 38 ASCA positivity in peptic ulcer

	GU	**DU**	**Total**
Open	11	23	34
Scar	2	2	4
Tatal	13	25	38

Next, we evaluated the correlation between *H. pylori* and ASCA in 128 peptic ulcer patients. The *H. pylori*–positive patients were 78 (60.9%). Thirty patients (38.4%) were ASCA positive in 78 *H. pylori* positive. Eight patients (16%) was ASCA positive in 50 *H. pylori* negative patients. The rate of ASCA positive in *H. pylori* positive was more significant than that in *H. pylori* negative patients (p<0.05). There was no significant difference of ASCA negative between *H. pylori* positive and negative (Table 3).

Table 3 Correlation between *H. pylori* and ASCA in peptic ulcer patients

	ASCA (+)	**ASCA (-)**	**Total**
H. pylori (+)	30	48	78
H. pylori (-)	8	42	50
total	38	90	128

In 104 non-peptic ulcer patients, we assessed the correlation between *H. pylori* and ASCA. Thirteen patients were ASCA-positive (12.5%) of 104 non-peptic ulcer patients. The *H. pylori*–positive patients were 30 (28.8%). Only four patients (13.3%) were ASCA positive in 30*H. pylori* positive. Nine patients (12.1%) was ASCA positive in 74*H. pylori* negative patients. Compared with peptic ulcer population, the rate of ASCA positivity in no peptic ulcer patients is low and there was no difference of ASCA positive between *H. pylori* positive and negative (Table 4).

Table 4 Correlation between *H. pylori* and ASCA in no peptic ulcer patients

	ASCA (+)	**ASCA (-)**	**Total**
H. pylori(+)	4	26	30
H. pylori(-)	9	65	74
total	13	91	104

Ten peptic ulcer-patients with *H.pylori* infection of 128 patients were treated with eradication therapy. The three patients of ten patients had ASCA positivity before *H. pylori* eradication. All ten patients succeeded in *H. pylori* eradication and no side effect was occurred. In every 3 patients with ASCA positive before eradication therapy, ASCA values changed positive to negative at 6 months after treatment. ASCA positivity was found to be correlated with eradication (Table 5).

Table 5 *H. pylori* eradication effect of ASCA

	before	**after**
H. pylori(+)	10	0
ASCA(+)	3	0

4. Discussion

This is the first report of the positive relationship between peptic ulcer and ASCA. Our results showed that active peptic ulcer with *H. pylori* infection have higher positivity of ASCA. After eradication successfully, the ulcer status were scar and the values of ASCA were deceasing compared to *H. pylori* infection.

Previous reports have shown a negative relationship between ASCA and *H. pylori* [12]**.** However, our results show a positive correlation between ASCA and *H. pylori*. Furthermore, ASCA was also associated with peptic ulcers. This reason may be that the mucosal tissue defect of an ulcer allows many antigenic substances, including fungi, to enter the tissue, and antibodies are produced by immune cells such as B cells to counter these foreign enemies. As the ulcer heals and becomes scarred, the influx of antigens into the tissue also decreases, and antibody production also decreases. Mucosal permeability increase in open ulcer stage and immunological reaction may be occurred high frequency. After eradication of *H. pylori*, mucosal permeability also decrease in ulcer scar status. The fact that ASCA is more positive in duodenal ulcers than in gastric ulcers may be related to the fact that the duodenum is histologically similar to the small intestine and that the small intestine has a higher absorption function from the gastrointestinal mucosa than the stomach. However, in our study cases, we did not completely exclude Crohn's disease, so it is possible that Crohn's disease may be associated with peptic ulcers. This is because Crohn's disease may well cause gastric or duodenal lesions. However, the definition of Crohn's disease itself is not based on definitive laboratory data, and further research data are needed to make this assessment.

The positive correlation between *H. pylori* and ASCA is due to the fact that *H. pylori* infection is a peptic ulcer aggravating factor [13]. This is consistent with our results in the present study, in which ASCA-positive cases were no longer observed after eradication of *H. pylori*. However, the presence of *H. pylori* does not necessarily indicate the presence of a peptic ulcer, and the percentage of ASCA-positive cases in negative peptic ulcer cases does not differ significantly between *H. pylori* and *H. pylori* cases.

The increase in ASCA positivity may also be related to the patient's diet. The diet centered on bread made with yeast is spreading in Japan, and there is a high possibility that ASCA is produced using yeast as an antigen. It is also possible that ulcers may be aggravated due to exacerbation of inflammation caused by allergies to yeast as an antigen [14]. Since we did not analyze these points in this study, the details of the causal relationship are not clear at this time. Further studies on the relationship between diet and ASCA and yeast exacerbation of gastrointestinal inflammation are needed.

While bacterial tests for *H. pylori* and imaging tests for peptic ulcer are limited, ASCA may be an effective biomarker that even takes disease activity into consideration, and further development of ASCA research is highly desirable in the future.

We mention here the limitations of our study. We have not examined the relationship between virulence of *H. pylori* and ASCA in the present study. Although *H. pylori* possesses virulence factors such as cagA and vacA, each strain of *H. pylori* possesses different virulence factors, and diversity is recognized [15]. Therefore, ASCA positivity may be increased in highly pathogenic cagA-positive and vacA-positive strains. Future studies are needed to clarify this point.

5. Conclusion

Our result demonstrated that that ASCA is associated with both peptic ulcers and *H. pylori* infection. Although, it is possible that ASCA is produced by immune cells due to peptic ulcers, the reason for generation of ASCA in

gastrointestinal disorder remains unclear. It is desired to develop a novel biomarker for *H. pylori* related peptic ulcer using ASCA.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors declare no conflict of interest of regarding the publication of this paper.

Statement of ethical approval

Permission for the study was received from our institution.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study

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