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ORIGINAL ARTICLE

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Gastrointestinal disorder and *Helicobacter pylori* infection in patients with rheumatoid arthritis

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Abstract Gastrointestinal disorders such as gastritis and peptic ulceration are very common in patients with rheumatoid arthritis. *Helicobacter pylori* appeared to be a high risk factor for the development of peptic ulcers or chronic active gastritis. Thus, the objective of this study is to elucidate gastrointestinal findings and the prevalence of *H. pylori* in patients with rheumatoid arthritis. Consecutive RA patients were recruited for this study, irrespective of gastrointestinal symptoms. Routine endoscopy was performed and mucosal specimens were analyzed according to the Sydney system. *H. pylori* infection was determined histologically using H–E staining, Wartin Starry silver staining, and immunohistochemistry. Of 97 patients, only 16 had gastrointestinal symptoms. By endoscopic examination, gastritis was observed in 39 patients (40.2%), gastric ulcers in 24 patients (24.7%), and duodenal ulcers in 7 patients (7.2%). The histological results analyzed by the Sydney system showed "inflammation," "active," and "atrophy" for 71.1%, 58.5%, and 54.6% of samples, respectively. Sixty patients (61.9%) were infected by *H. pylori*, but the presence of *H. pylori* did not increase the chance of endoscopic gastrointestinal disorders. The presence of a rheumatoid factor was inversely related to *H. pylori* infection, and the value of the rheumatoid factor was lower in patients with the infection. In conclusion, it was found that *H. pylori* infection was not a major cause of gastrointestinal disorders in RA, and that the presence of rheumatoid factor significantly reduces the chance of *H. pylori* infection.

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Introduction

Gastrointestinal (GI) lesions have a major adverse effect on long-term nonsteroidal anti-inflammatory drug (NSAID) users. From the results of the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) study, Singh and Ramey[1] concluded that serious GI ulcer complications were not heralded by previous symptoms, and that acid reduction therapy, including H2-receptor antagonist, was of little benefit. In patients with rheumatoid arthritis (RA) who were usually treated with NSAIDs, the annual rate of hospitalization was 1.46% and the annual death rate was 0.22% of patients with GI complications.[1]

Helicobacter pylori infection was believed to be a high risk factor for the development of peptic ulcers[2] or chronic active gastritis.[3] Although conflicting results on whether the presence of *H. pylori* exacerbates NSAID-related gastrointestinal disorders[4–9] were reported, a well-controlled prospective study showed that eradication of *H. pylori* prior to NSAID use decreases the chances of developing ulcers.[10]

Chronic NSAID users are common among patients with RA, who very often also have gastrointestinal disorders. The aim of this study is to evaluate the gastric mucosal lesion and *H. pylori* status in RA patients.

Patients and methods

Patients

Ninety-seven consecutive patients, who fullfilled the ACR criteria for RA[11] and agreed to participate in this study, were recruited from our clinic, with informed consent, irrespective of the presence of GI symptoms. There were 11 men and 86 women, with a mean age of 59.6 years and an

average disease duration of 18.6 years (Table 1). All of the patients were treated with prednisolone and/or NSAIDs. Seventy-eight (80.4%) patients were treated with prednisolone (≦7.5 mg/day) and 82 (84.5%) patients were treated with NSAIDs. Seventy-nine (81.4%) patients were taking gastrointestinal medication, including H2-receptor antagonists and/or mucoprotectives. None of the patients had received eradication therapy for *H. pylori*. The patients were asked whether they had GI complaints such as abdominal pain, heart burn, nausea, or dyspepsia.

Endoscopic examination

Routine gastroduodenal endoscopies were performed. At that time, three mucosal specimens were taken from the greater curvature of the lower antrum, the greater curvature of the upper body, and the lesser curvature of the lower body for histological evaluation.

Histological study

Biopsied specimens were stained with hematoxilin–eosin (H–E), and the results were evaluated according to the Sydney system.[12] The Sydney system is a classification of gastritis developed to provide accurate and uniform documentation in order to compare data between medical centers when *H. pylori* appears to be a major cause of gastritis. The System relies on adequately biopsied clinical materials. Morphological indices (inflammation, activity, atrophy, metaplasia, and density of *H. pylori*-like organisms) that are considered important in monitoring the natural history and therapeutic regimen were graded as none, mild, moderate, or severe. To confirm the presence of *H. pylori*, Wartin Starry silver stain and immunohistochemical stain using the avidin–biotin complex method with polyclonal anti-*H. pylori* antibody (DAKO) were used (Fig. 1).

Table 1. Characteristics of patients

Sex		Age (years)			Disease duration (years)		
Male	Female	<40	41–60	61<	<5	6–15	16<
11	86	3	48	46	9	33	55

Statistical analysis

Clinical and laboratory data of patients who were *H. pylori*-positive and those who were *H. pylori*-negative were analyzed using the Mann–Whitney *U*-test, the χ^2 test, or Fisher's exact probability test.

Results

Clinical symptoms

Of 97 patients, only 16 had gastrointestinal symptoms. No difference in symptoms was found between patients with and without *H. pylori* infection.

Endoscopic findings

Gastritis (erosion, bleeding, edema, or erythema) was observed in 39 patients (40.2%) and peptic ulcers in 28 patients (28.9%), including gastric ulcers in 24 (24.7%) and duodenal ulcers in 7 (7.2%). The presence of *H. pylori* was determined by histological examination using three mucosal specimens, as described above. In 49 out of 60 positive patients, *H. pylori* was observed in more than two specimens.

Sixteen out of 60 patients (26.7%) with *H. pylori* infection and 8 out of 37 patients (21.6%) without *H. pylori* infection had gastric ulcers, with no significant differences. The gastric ulcers were located in the antrum in all of the

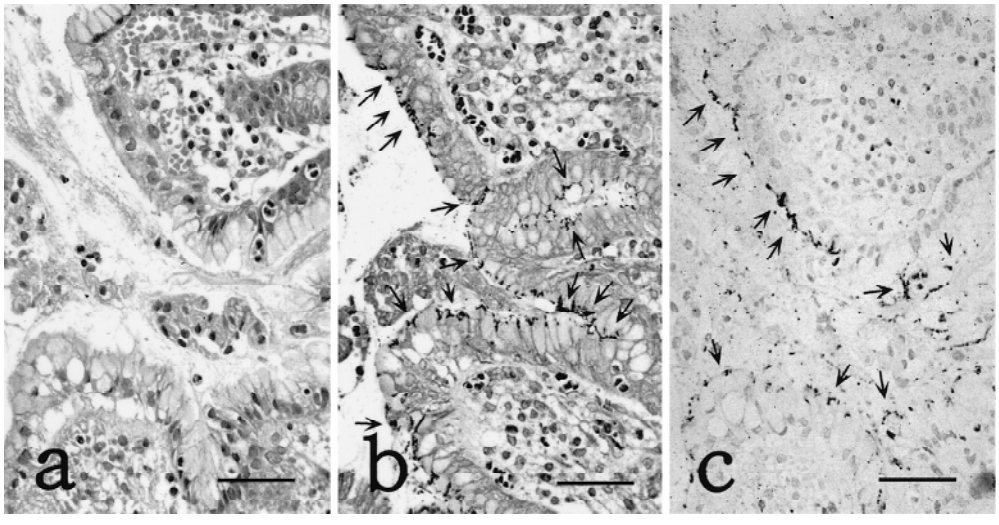

Fig. 1. Histological detection of *H. pylori* by (**a**) hematoxylin–eosin dye, (**b**) Wartin–Starry dye, and (**c**) immunohistochemical staining. *Arrows* show a group of *Helicobacter pylori* organisms. *Bar* = 50 μm

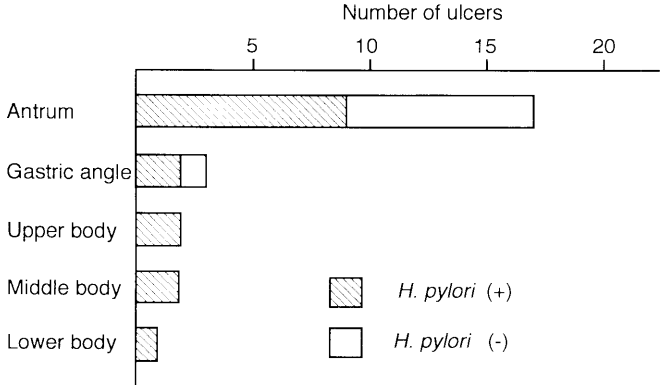

Fig. 2. Location of gastric ulcers in patients with or without *H. pylori* infection. Most ulcers in *Helicobacter pylori*-negative patients were located in the antrum, whereas ulcers in *Helicobacter pylori*-positive patients were located in the gastric body

Table 2. Endoscopic findings in patients with rheumatoid arthritis and the relationship with *Helicobacter pylori* infection

	Total	*Helicobacter pylori*	
		+	−
n	97	60	37
Abnormal findings	69 (71.1%)	39 (65.0%)	30 (81.1%)
Gastritis	39 (40.2%)	18 (30.0%)	21 (56.8%)
Gastric ulcer	24 (24.7%)	16 (26.7%)	8 (21.6%)
Duodenal ulcer	7 (7.2%)	3 (5.0%)	4 (10.8%)
Polyp	9 (9.3%)	6 (10.0%)	3 (8.1%)
Amyloidosis	2 (2.1%)	1 (1.7%)	1 (2.7%)
Other	7 (7.2%)	4 (6.7%)	3 (8.1%)
No abnormal findings	28 (28.9%)	21 (35.0%)	7 (18.9%)

patients without *H. pylori*, including one who also had an ulcer in the gastric horn. However, ulcers were also found in the gastric body in patients with *H. pylori* (Fig. 2). For unknown reasons, normal findings were observed more frequently in *H. pylori*-positive patients. Only 18 patients (30.0%) with *H. pylori* infection had gastritis, whereas 21 patients (56.8%) without *H. pylori* infection had gastritis. Twenty-one patients (35.0%) with *H. pylori* infection showed no abnormal endoscopic findings, and only 7 patients (18.9%) without *H. pylori* infection showed no abnormal findings (Table 2). These findings at least suggest that *H. pylori* infection is not a major cause of gastrointestinal lesions in RA patients.

Histological findings

The histological results analyzed by the Sydney system showed "inflammation," "active," and "atrophy" for 71.1%, 58.5%, and 54.6% of the samples, respectively (Fig. 3). The histological findings were inconsistent with both the presence of clinical symptoms and endoscopic findings. Chronic active gastritis rated as "active" in the Sydney system, and characterized by the infiltration of neutrophil polymorphs, was strongly related to *H. pylori* infection.

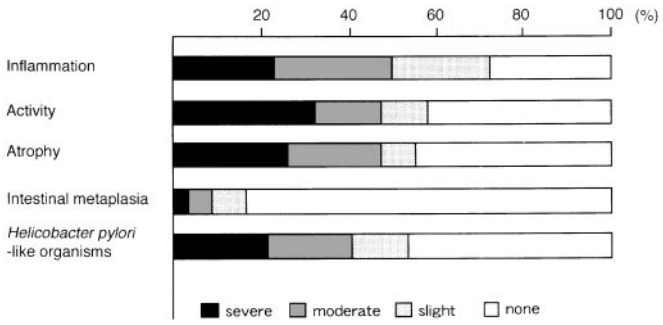

Fig. 3. Histological findings in patients with rheumatoid arthritis assessed by the Sydney system with routine hematoxylin–eosin staining

Table 3. Clinical and laboratory findings in RA patients with and without *Helicobacter pylori* infection

	Helicobacter pylori		*P*
	+ (n = 60)	− (n = 37)	
Sex (M:F)	6:54	5:32	
Age (years)	59.6 ± 7.8	59.5 ± 10.8	ns
Duration (years)	17.6 ± 10.6	20.1 ± 10.5	ns
ESR (mm/h)	41.9 ± 23.4	41.6 ± 27.4	ns
CRP (mg/dl)	1.25 ± 1.5	1.71 ± 2.02	ns
RF (IU/ml)	97.2 ± 140.5	250.8 ± 258.0	<0.005
RF(+):RF(−)	21:39	30:7	<0.001

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor
Values are presented as mean ± SD and number of patients
Analyzed by the Mann–Whitney *U*-test and the χ^2 test

Helicobacter pylori infection

Sixty out of 97 patients (61.9%) were infected by *H. pylori* as estimated by histological methods (H–E stain, Wartin Starry silver stain, and immunohistochemistry). In the comparison of clinical and laboratory findings, there was a significant difference between patients with and without *H. pylori* infection only in the rheumatoid factor (RF). The average RF values were lower in the patients who were infected by *H. pylori*. Thirty out of 37 (81.1%) *H. pylori*-negative patients were positive for RF, whereas only 21 out of 60 (35.0%) *H. pylori*-positive patients were positive for RF (Table 3). This indicated an inverse relationship between the presence of RF and *H. pylori* infection. With the exception of sulfasalazine (SSZ), neither antirheumatic drugs nor mucosal protective drugs, including H2 receptor antagonists and antacids, affected *H. pylori* status (Table 4).

Discussion

In this study, 71% of patients had endoscopically abnormal findings. Up to 24.7% of patients in our study had gastric ulcers, whereas this value was 15.5% in the study carried out by the Japanese Rheumatism Foundation.[13] It was con-

Table 4. Comparison of medication in rheumatoid patients with and without *Helicobacter pylori* infection

	H. pylori		*P*
	+ (n = 60)	− (n = 37)	
Medication			
Corticosteroids	48	30	ns
NSAIDs	53	29	ns
DMARDs			
Gold sodium thiomalate	1	4	ns
Sulfasalazine	12	2	<0.05
Methotrexate	28	19	ns
Bucillamine	21	17	ns
Antiulcer			
H2-blockers	14	7	ns
Mucoprotectives	46	30	ns

Comparison between *H. pylori*-positive and -negative results was analyzed by the χ^2 test or Fisher's exact probability test

sidered that one reason for the difference was that patients in this series had a longer disease duration than those in the other study, suggesting that they had taken a larger amount of drugs for the treatment of RA. Another possible reason is that patients who had history of GI involvement were more likely to participate in this kind of study. As Tytgat[14] commented, the correlation between endoscopic appearance and histology is poor, and there was no significant relationship between endoscopic findings and histological results, including *H. pylori* infection, in this study (data not shown).

The prevalence of *H. pylori* infection differed with respect to age, race, and economic status. The frequency increased with age, and was inversely correlated with socioeconomic status. However, there was no association between *H. pylori* infection and the consumption of alcohol, NSAID use, or smoking.[15] About 70%–80% of Japanese people who are over 40 years old are infected with *H. pylori*.[16] Upadhyay et al.[17] and Goggin et al.[18] reported that 50% of patients with RA were infected by *H. pylori*, and the prevalence was similar to that expected for an age-matched population. On the other hand, Caselli et al.[19] reported a low prevalence of *H. pylori* infection, and concluded that this was caused by the use of NSAIDs. These authors also reported the minimal inhibitory concentration (MIC) of NSAIDs against *H. pylori*. Matsuhisa et al.[20] also reported that the prevalence of *H. pylori* was significantly lower in patients with RA than in matched controls. Goggin et al.[18] speculated that the underestimation of the reported prevalence was caused by the use of a single method to detect *H. pylori*. In this study, direct evidence of *H. pylori* infection was obtained from three given sites in the stomach, and three different stains were performed on each sample to ensure that the diagnosis was correct.

We investigated the factors that discriminated between RA patients infected by *H. pylori* and those who were not. The results showed that RF values were significantly higher in *H. pylori*-negative patients than in *H. pylori*-positive patients. Gender, age, disease duration, and disease activity of RA did not affect *H. pylori* status.

Intramuscular gold sodium thiomalate (GST) for the treatment of rheumatoid arthritis was reported to decrease the prevalence of *H. pylori* as GST had a bactericidal effect.[21] We had only five patients who were being treated with intramuscular GST. Although the differences were not significant, only one of them was infected with *H. pylori*. Interestingly, patients treated with SSZ had a slightly higher prevalence of *H. pylori* infection. Proton pump inhibitors such as omeprazole, which have a suppressive effect on *H. pylori* colonization,[19] were not used in the patients in this study. No significant differences were found regarding *H. pylori* status between patients treated by H2 receptor antagonists and those who were not. We did not find any further differences between patients who were infected with *H. pylori* and those who were not in regard to their medication.

One of the possible factors which affected *H. pylori* infection was the presence of RF. RF is an autoantibody against the Fc portion of IgG and is usually detected in RA sera, and is sometimes found with other autoimmune diseases such as systemic lupus erythematodes, infectious diseases, and liver disorders. RF is also detected in a small percentage of healthy people, and the prevalence of a positive test for RF increases with age. In this study, none of the patients had infectious diseases or liver disease, and there was no significant difference between the mean age of *H. pylori*-positive and -negative patients. Thus, the low prevalence of *H. pylori* may be explained as follows. It is possible that RF itself affects *H. pylori* either directly or through its environment, causing an inhibition of its growth. RF is one of the factors predicting a poor prognosis.[23] Patients with a high RF titer would have a history of taking a larger amount of antirheumatic drugs, including NSAIDs, which might affect the survival of *H. pylori*.

In conclusion, in contrast to the general belief that *H. pylori* is a major cause of ulcers and dyspeptic syndromes,[24] it did not aggravate gastrointestinal disorders in patients with RA, and the presence of rheumatoid factor was found to be a significant factor in reducing the chance of *H. pylori* infection.

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