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CORRELATION BETWEEN *HELICOBACTER PYLORI* INFECTION AND PULMONARY WEGENER'S GRANULOMATOSIS ACTIVITY

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Wegener's granulomatosis is a clinicopathologic entity of unknown origin characterized histologically by necrotizing granulomatous angiitis that affects any organ system. The disease most commonly involves the upper and lower respiratory tract and kidneys. Wegener's granulomatosis is a disease which requires a long-term use of steroids and NSAIDs. Because of that patients frequently develop gastroduodenal mucosal lesions and concurrent *Helicobacter pylori* infection. The aim of the study was to assess the impact of *H. pylori* infection on clinical features in patients with Wegener's granulomatosis treated with non-steroidal anti-inflammatory drugs, steroidal drugs, and cyclophosphamide. Thirty six patients with systemic Wegener's granulomatosis were tested for the presence of *H. pylori* infection and 25 of them turned up *H. pylori* positive. The severity of Wegener's granulomatosis disease, prevalence of gastroduodenal lesions, and the type and duration treatment seem to depend upon *H. pylori* infection.

Key words: *Helicobacter pylori, infection, Wegener's granulomatosis*

INTRODUCTION

Wegener's granulomatosis is a clinico-pathologic entity of unknown origin characterized histologically by necrotizing granulomatous angiitis that may affect any organ system. The disease most commonly involves the upper and lower respiratory tract and kidneys (1). Wegener's granulomatosis is a disease which requires a long-term use of steroids and NSAIDs. Because of that patients frequently develop gastroduodenal mucosal lesions and concomitant *Helicobacter pylori* infection (2, 3). *H. pylori* is a gram-negative, microaerophilic

bacterium that infects various areas of the stomach and duodenum. The bacterium's helical shape is thought to have evolved to penetrate and favor its motility in the mucus gel layer. Many cases of peptic ulcers, gastritis, duodenitis, and cancers are caused by *H. pylori* infection (4, 5). However, many who are infected do not show any symptoms of disease. Infection may be symptomatic or asymptomatic. It is estimated that up 70% of infection is asymptomatic and about 2/3 of the world population are infected by the bacterium, making in the most widespread infection in the world. Actual infection rates vary from nation to nation; with rates around 25% in Western Europe and North America and much higher in the Third World (5). The bacteria have been isolated from saliva, dental plaque, and feces of infected patients, which indicates gastro-oral or fecal-oral way as possible transmission routes (5). *H. pylori* produces large amounts of urease enzymes which are localized inside and outside of the bacterium. Urease metabolizes urea to carbon dioxide and ammonia. The survival of *H. pylori* in the acidic stomach environment is dependent on urease. The ammonia that is produced is toxic to the epithelial cells, and along with the other products of *H. pylori* such as proteases, phospholipases, and catalases, causes damage to these cells. Some strains of the bacterium have as particular mechanism for 'injecting' the inflammatory inducing agent peptydoglycan from their own cell wall into the epithelial stomach cells. This factor may play a role in allowing certain strains to invade host tissue (5).

Patients with Wegener's granulomatosis, other vasculitides, and rheumatic diseases who are treated with non-steroidal anti-inflammatory drugs (NSAIDs) and steroidal anti-inflammatory ones are at increased risk of developing upper gastrointestinal mucosal damage (6-8). This gastrointestinal damage varies from gastritis and erosions to gastric and duodenal ulcers and their life-threatening complication (bleeding and perforation). The role of *H. pylori* in the pathogenesis of NSAIDs and steroid-inducted gastrointestinal lesions remains controversial. Much evidence has accumulated for a pathogenetic role of *H. pylori* in the development of chronic gastritis.

The present study was undertaken to verify the potential impact of *H. pylori* infection on gastroduodenal lesions in patients with Wegener's granulomatosis. We addressed this issue by attempting to correlate *H. pylori* infection with clinical symptoms, laboratory data, and treatment used in Wegener's granulomatosis.

MATERIAL AND METHODS

The study was approved by a local Ethics Committee. Informed consent was obtained from all patients examined. The study was performed in 36 patients with pulmonary Wegener's granulomatosis (24 female, 12 male, mean age 44.3 years, from the Primary Systemic Outpatients Clinic Czerniakowski Hospital, Warsaw Medical University in Warsaw, Poland. Wegener's granulomatosis has been diagnosed between 1998 and 2007 on the grounds of usually standing

criteria, i.e., the assessment of disease process progression, serological assessment (ANCA antibodies titers), and histopathological examination.

The serological test for detection of ANCA antibodies has been performed using the indirect immunofluorescence (IIF) and immunoensimatic methods (ELISA). Treatment was introduced after obtaining consent. The patients were treated with immunosuppressive drugs (prednisone and cyclophosphamide orally). All patients fulfilled the American College of Rheumatology classification criteria, the Chapel Hill Consensus Conference definition, and also the EUVAS ANCA-associated vasculitis definition for Wegener's granulomatosis. At the time of the study 34 patients were ANCA positive. The patients were under Outpatient Clinic care and received follow-up clinical, laboratory, pulmonary function, and chest radiographic examinations. The clinical scoring (BVAS-Wegener's granulomatosis index and DEI index) and endoscopic examination were the basis of this study. All patients were treated with a typical induction regiment consisting of prednisolone and cyclophosphamide orally for at least 2 month; 25 patients took a single oral dose of NSAIDs (ibuprofen or naproxen). Upper gastrointestinal endoscopy was performed, regardless of gastrointestinal symptoms, after patient's permission. The endoscopic examination was performed with a gastroscope (GIF E or GIF V2 Olympus, Japan) by two endoscopists. During each endoscopic examination a total of seven biopsy specimens were obtained from the gastroduodenal mucosa: three specimens from the greater curvature, three from the antrum and one from the duodenum. Six specimens were used for histological investigations and one for a rapid urease test (CLO-test). Biopsy specimens for histology were fixed in 10% buffered formalin, embedded in paraffin, and sectioned at 5 μm. The sections were stained with hematoxylin-eosin and Giemsa stain for the histological detection of *H. pylori*. *H. pylori* infection was determined to be positive when CLO-test and histology examination revealed positive results. Otherwise, the patients were regarded as negative for *H. pylori* infection. Histological analysis of the background gastric mucosa was based on the updated Sydney system, according to the degree of atrophic changes: none, mild, moderate, or marked. In each case, the most marked degree of atrophic changes from, at least, the two specimens was regarded as a representative grade of destruction.

In addition, we analyzed: age, gender, gastrointestinal symptoms, disease activity (DEI, BVAS-Wegener's granulomatosis indexes), biochemical and serological data, duration of corticosteroids treatment, duration of NSAIDs treatment, and the type of gastroprotective drugs - histamine H_2 (H_2) receptor antagonists or proton pomp inhibitors (PPI).

Statistical analysis

The Mann-Whitney U and Fisher tests were used for comparison between groups. $P<0.05$ was considered to be statistically significant. Statistical elaboration was performed with an SAS commercial software.

RESULTS

The overall prevalence of *H. pylori* infections in the Wegener's granulomatosis our patients was 71.4%; 25 patients were *H. pylori* positive and 11 patients were negative. *Table 1* presents a comparison of clinical and endoscopy findings between *H. pylori* positive and negative patients. No gastric cancer was revealed. *Table 2* summarizes the clinical features of Wegener's granulomatosis in both groups. Clinical activity (BVAS-Wegener's granulomatosis, DEI indexes) was higher in the *H. pylori* positive group.

Laboratory parameters such as: WBC, ESR, CRP, PLT, and ANCA titers were all higher in this group. On the other side, hemoglobin concentration and the value of glomerular filtration rate were higher in the *H. pylori* negative group. *Table 3* presents the medications used for Wegener's granulomatosis and the gastroprotective treatment in both group.

All patients from the *H. pylori* positive group received NSAIDs over a period of, at least, 1 month and H_2 antagonist as a gastroprotective drug over a period of, at least, 1 month. Mild gastric mucosal atrophy in Wegener's granulomatosis patients with *H. pylori* positive infection was observed in 48.1% of patients, moderate in

Table 1. Comparison of baseline and endoscopy findings between *H. pylori* positive and negative patients with Wegener's granulomatosis.

	H. pylori Positive patients (n=25)	*H. pylori* Negative patients (n=11)	P
Age (years), median (range)	61 (29-84)	54 (24-68)	0.07
Male/female	9/16	5/6	0.07
Smokers, n (%)	12 (48%)	5 (45%)	0.07
Drinkers, n (%)	9 (36%)	3 (27%)	0.03
BVAS-WG	14 (12-24)	6 (5-11)	0.04
DEI	6 (9-11)	3 (4-6)	0.03
Gastroduodenal lesion	22 (88%)	9 (82%)	0.001
Gastritis in endoscopy	21 (84%)	5 (45%)	0.01
Duodenitis in endoscopy	4 (16%)	3 (27%)	0.02
Gastric ulcer in endoscopy	15 (60%)	6 (55%)	0.0001
Duodenal ulcer in endoscopy	1 (4%)	2 (18%)	0.06

Table 2. Clinical and biochemical features in Wegener's granulomatosis patients.

	H. pylori Positive patients (n=25)	*H. pylori* Negative patients (n=11)
Disease duration (years), median (range)	5.1 (0.8-7.8)	4.2 (0.4-8.4)
Laboratory data, median (range)		
ESR (mm/h)	48 (10-120)	39 (8-114)
CRP (mg/dl)	5.5 (0.5-38)	1.65 (1.0-22.4)
WBC (cells/µl)	8.5 (3.8-16.5)	7.9 (3.4-16.8)
PLT (cells/µl)	218.4 (91.4-370.5)	180.5 (110.0-420.5)
HgB (g/%)	10.9 (6.9-13.4)	11.5 (7.8-14.1)
GFR (ml/min)	68.4 (46-121)	70.6 (54-118.6)
cANCA titer	1:640 (1:80-1:2250)	1:320 (1:40-1:1250)

Table 3. Comparison of medications used between *H. pylori* positive and negative groups.

Regimen	*H. pylori* Positive patients (n=25)	*H. pylori* Negative patients (n=11)
Therapies for WG		
NSAID + glucocorticosteroid	2 (8%)	1 (9%)
NSAID + glucocorticosteroid+ cyclophosphamide	16 (64%)	2 (18%)
NSAID + corticosteroid + azathiopyrine	7 (28%)	9 (82%)
Gastroprotective drugs	0 (0%)	0 (0%)
H_2 receptor antagonist	21 (84%)	4 (36%)
PPI	4 (16%)	10 (91%)
Mucosal protective drugs	4 (16%)	5 (45)
Duration of NSAID use (years) median (range)	5.3 (0.4-8.2)	3.6 (0.2-9.4)
Duration of glucocorticosteroid use (years) median (range)	1.8 (0.6-2.2)	1.45 (0.3-1.2)

PPI – proton pump inhibitors.

35.3%, and marked in 7% of patients. In contrast, 92% of the patients negative for *H. pylori* infection had no gastric mucosal atrophy, and in the remaining negative for *H. pylori* patients, the signs of mucosal atrophy were never marked.

DISSCUSION

In the present study we observed that *H. pylori* infection caused clinical symptoms and gastroduodenal mucosal lesions in patients with Wegener's granulomatosis. The prevalence of *H. pylori* infection was 71.4% in Wegener's granulomatosis and 61.4% in rheumatoid arthritis patients (10). According to some epidemiological and clinical investigations, the difference in the prevalence of *H. pylori* infection among patients with Wegener's granulomatosis, with other types of vasculitis, and the general population is insignificant (7, 8). The possible interaction of NSAIDs and *H. pylori* in the pathogenesis of gastroduodenal lesions is still uncertain. NSAIDs can be a strong factor which causes the mucosal destruction, especially during concomitant treatment with steroids and cyclophosphamide, which was seen in the patients of this study. On the other side, there are reports that show that *H. pylori* infection does not influence the endoscopic grade of gastroduodenal mucosal lesions in patients using NSAIDs for a long time (9). A rapid development of selective COX-2 inhibitors (COXIB), as a safe alternative to NSAIDs might implications for the incidence of gastrointestinal damage. In fact, *H. pylori* infection might become the major cause of peptic ulceration in COXIB users.

In the present study, the incidence of dyspeptic syndrome and the intensity of gastroduodenal lesions were different between the *H. pylori* positive and negative groups, which is at variance with the rheumatoid arthritis patients described in a study by Ishikawa *et al* study (10). *H. pylori* infection contributes to the pathogenesis of gastroduodenal lesions and reflux oesophagitis in patients who receive NSAIDs. Zentilin *et al* (11) have reported the effect of *H. pylori* eradication on the severity of arthropathy in patient with rheumatoid arthritis. Ishikawa *et al* (10) have found no difference in the clinical severity of rheumatoid arthritis between *H. pylori* positive and negative patients, which is opposite to our present study.

A suppressive effect on *H. pylori* infection of glucocorticosteroids used in rheumatoid arthritis patients has been reported (12). Glucocorticosteroids might potentially act bacteriostatically against *H. pylori*, but our present results suggest that they do not decrease the prevalence of *H. pylori* infection in Wegener's granulomatosis patients. The reverse, the effect of drugs intended to eradicate *H. pylori* on the main disease activity has not been substantiated either (12).

Concluding, our results show that *H. pylori* infection seems associated with Wegener's granulomatosis activity and gastroduodenal mucosal lesions in patients who undergo a complex therapy with glucocorticosteroids, cyclophosphamide, and NSAIDs. There seems to be evidence to suggest the necessity for *H. pylori* eradication in patients with Wegener's granulomatosis, since the bacterium is a chronic source of infection during the disease course and can be a potential relapse factor (13-16).

Today, the standard triple therapy to eradicate *H. pylori* is amoxicillin, clarithromycin, and a proton pomp inhibitor (17, 18). A meta-analysis of randomized controlled trials suggests that supplementation with probiotics can improve eradication rates and reduce adverse events. Unfortunately, an increasing number of infected individuals are found with antibiotic-resistant bacteria. The resistance results in initial treatment failure and requires additional rounds of antibiotic therapy or alternative strategies (19, 20).

Conflicts of interest: No conflicts of interest were declared by the authors in regard to this work.

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