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CLINICAL REPORT

Rosacea: A Cutaneous Marker of *Helicobacter pylori* Infection? Results of a Pilot Study

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Given the long purported anecdotal association between rosacea and gastrointestinal disease, the discovery that *Helicobacter pylori* causes gastritis and duodenal ulcer disease has led to a hypothesized role for this organism in the aetiology of rosacea. We conducted a case-series study of 49 patients to assess the potential association between severity of rosacea and direct and serological evidence of *H. pylori* infection. Patients were classified by severity into non-inflammatory erythematotelangiectatic or inflammatory/papulopustular rosacea and were tested for current *H. pylori* infection and evidence of previous exposure. Positive ^{13}C-urea breath test and ELISA tests were more likely to be observed in patients with inflammatory rosacea, although not statistically significantly so (OR = 3.0, $p = 0.15$ and OR = 2.9, $p = 0.16$, respectively). However, the proportion of patients who tested positive in both assays (versus negative in at least one) was even higher in the inflammatory rosacea group and neared statistical significance (OR = 4.5, $p = 0.06$). This pilot study provides sufficient evidence suggestive of a positive association between the severity of rosacea and the presence of *H. pylori* to warrant further research.
Key words: rosacea;* Helicobacter pylori*; ELISA; ^{13}C-urea breath test.

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An association between rosacea and gastrointestinal disease was considered as long ago as 1920, when achlorhydria and hypochlorhydria were thought to be predisposing factors (1). However, attempts to confirm such an association have been unsuccessful (2, 3). The discovery that the Gram-negative bacterium *Helicobacter pylori* is the cause of gastritis and duodenal ulcer disease has led to a hypothesized role in the aetiology of rosacea. Based on case-series studies of rosacea, several authors have reported higher than expected *H. pylori* seroprevalence (4, 5) and antibody titres (6), and have commented on improvement in the dermatological condition following *H. pylori* eradication therapy (4, 5, 7–11). Yet other studies have failed to confirm this relationship (12–16).

We report the results of a case-series pilot study designed to further investigate the potential association between the severity of rosacea and direct and serological evidence of concurrent *H. pylori* infection.

MATERIALS AND METHODS

Patients

Approval for the study was obtained from the local Research and Ethics Committee. Fifty-one consecutive patients attending a dermatology outpatient department over a period of 36 months and diagnosed by a single consultant dermatologist as having rosacea were invited to participate. The use of a single clinical evaluator was designed to reduce the potential for bias from interobserver variation (17).

For the purpose of investigating the potential for an increased association between prevalence of *H. pylori* and severity of rosacea, cases were classified according to the presentation and severity of their condition into two groups; those who had non-inflammatory disease, characterized by erythema and telangiectasia only, and those who also demonstrated inflammatory lesions such as papules and pustules. Diagnosis of rosacea and assessment of severity were made prior, and hence blind, to *H. pylori* bioassays. Referring general practitioners were subsequently informed of *H. pylori* bioassay results for all patients.

In consideration of a previously identified age-dependent increase in *H. pylori* infection (18) and seroprevalence (19) and a greater risk of rosacea in women than in men (20), it was considered imperative to control for age and gender in all subsequent statistical analyses.

Bioassays

Each study participant underwent a ^{13}C-urea breath test (^{13}C-UBT – B.S.I.A. Ltd, Brentford, Middlesex, UK). The ^{13}C-UBT is a highly specific (>95%) and very sensitive (>90%) non-invasive assay which detects the presence of an active *H. pylori* infection (21). The assay is based on spectrophotometrically demonstrating a significant increase in exhaled ^{13}C-labelled carbon dioxide produced by bacterial metabolism following a test meal containing ^{13}C-labelled urea.

Serological evidence of *H. pylori* infection was sought using an enzyme-linked immunosorbent assay (ELISA – VIVA Diagnostika GmbH, Huerth/Cologne, Germany) to detect IgG antibodies to the 120 kD (Cag A) antigen of *H. pylori*.

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The ELISA provided a semi-quantitative assessment of antibody levels, since colorimetric development was determined relative to a set of positive and negative control sera as negative, intermediate positive and strong positive. The sensitivity and specificity of *H. pylori* serological assays range from 88% to 99% and 86% to 95%, respectively (22). All ELISAs were read by the same operator, blind to rosacea status.

Statistical analysis

Standard statistical methods, including ordinary logistic regression, were utilized to generate odds ratios (OR) as measures of association when contrasting prevalence of bioassay results between erythemato-telangiectatic versus inflammatory/papulo-pusutular rosacea patients. All statistical analyses were conducted using the SAS® System for Windows release 8.01 statistical software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Demographic details of the rosacea patients are presented in Table I. Two of the 51 consecutively diagnosed patients with rosacea declined to participate in the study. There were no statistically significant differences for either gender ($p=0.62$) or age ($p=0.81$) by severity of rosacea.

Distribution of *H. pylori* bioassay results and measures of association for severity of rosacea, but controlling for age and gender, are presented in Table II. Overall, 45.5%

Table I. *Demographic data for the two groups of rosacea patients.*

		Age in years			
Rosacea severity	*n*	Mean	Median	Range	SD
No inflammatory lesions, erythematotelangiectatic only ($n=16$)					
Male	8	52.1	55	33 – 72	14.6
Female	8	51.8	51	29 – 80	18.9
Inflammatory, with papules and/or pustules present ($n=33$)					
Male	19	55.7	59	31 – 71	13.1
Female	14	44.2	44	28 – 69	11.4

Table II. *Results of analyses of association between rosacea severity and* H. pylori *bioassay results, where strength of association is expressed as age- and gender- adjusted odds ratio (and 95% confidence intervals) derived from logistic regression.*

	Rosacea severity						
	Erythematotelangiectatic[1] ($n=16$)		Inflammatory/papulopustular[1] ($n=33$)				
H. pylori Bioassays	*n*	%	*n*	%	Odds ratio[2]	(95% CI)	p[3]
^{13}C-urea breath test							
Negative	12	75.0	18	54.5	–		
Positive	4	25.0	15	45.5	3.0	(0.7 – 12.1)	0.15
ELISA							
Negative	5	31.2	5	15.2	–		
Intermediate positive[4]	4	25.0	11	33.3	2.9	(0.5 – 16.1)	0.22
Strong positive[4]	7	43.8	17	51.5	2.8	(0.6 – 14.5)	0.21
Total positive	11	68.8	28	84.8	2.9	(0.6 – 12.7)	0.16
Neither assay positive[5]	4	25.0	5	15.2	–		
One assay positive[5]	9	56.3	13	39.4	1.3	(0.3 – 6.7)	0.74
Both assays positive[5]	3	18.7	15	45.4	5.5	(0.8 – 39.6)	0.09
Neither or one positive[6]	13	81.3	18	54.5	–		
Both assays positive[6]	3	18.7	15	45.4	4.5	(0.9 – 21.9)	0.06

[1]Erythematotelangiectatic rosacea refers to signs of rosacea present in the absence of inflammatory lesions. Inflammatory rosacea is characterized by the additional presence of papules and/or pustules.
[2]Odds ratios are adjusted for age and gender, i.e. estimates are derived from models containing age and gender parameters.
[3]*P*-values are derived from likelihood-ratio tests, or, in the case of ELISA and combined interpretation, from approximate score based Wald chi-square estimates for each dummy variable.
[4]Intermediate and Strong positive are dummy variables for the ordinal ELISA scoring system and provide simultaneous contrasts relative to a negative ELISA result (i.e. the default intercept).
[5]Interpretation of ELISA and ^{13}C-urea breath test results combined where dummy variables for one or both assays positively provide simultaneous contrasts relative to negative results on both assays (i.e. the default intercept).
[6]Series interpretation of ELISA and ^{13}C-urea breath test results, i.e. where a patient is considered positive only if demonstrating a positive result on both assays.

(=15/33) of patients with inflammatory rosacea and 25.0% (=4/16) of those with only erythemato-telangiectatic rosacea exhibited a positive ^{13}C-UBT, yielding an adjusted OR of 3.0 ($p=0.15$). This suggestion of a positive association with rosacea severity was also noted for the detection of antibodies against *H. pylori* in ELISA, such that either an intermediate or strong positive test result was more likely to be observed in those with inflammatory rosacea, although not statistically significantly so (OR=2.9, $p=0.22$; OR=2.8, $p=0.21$, respectively). However, when the two assays were interpreted in series, patients with inflammatory/papulo-pustular rosacea were 4.5 times more likely to exhibit positive test results on both ^{13}C-UBT and ELISA versus at least one negative result (OR=4.5, $p=0.060$).

Neither age nor gender was significant in any tests of association with rosacea nor did their inclusion in analyses affect the magnitude or significance of parameter estimates of ^{13}C-UBT or ELISA covariates.

DISCUSSION

Investigations of a potential association between rosacea and *H. pylori* have yielded equivocal results. Table III provides a summary of recent publications on the subject. While Powell et al. (6) reported higher *H. pylori* antibody titres and Rebora et al. (4, 5) observed higher *H. pylori* seroprevalence in rosacea patients than the general population, these studies were uncontrolled. The majority of controlled studies (8, 13–16) showed no significant difference in either seroprevalence or direct demonstration of *H. pylori*. However, Szlachic et al. (9) and Szlachic (10) observed significantly higher prevalences of infection and serology in rosacea patients than in controls. It is notable that they studied rosacea patients "with visible papules and pustules associated with erythema and flushing on the face", corresponding to our definition of more severe inflammatory papulopustular rosacea. While the results of the current study did not achieve statistical significance, to the best of our knowledge this is the first suggestion of a potential positive association between the severity of rosacea and both concurrent *H. pylori* infection and magnitude of anti-*H. pylori* CagA antigen humoral immune response. Such a "dose-response" relationship is generally considered supportive evidence of causality (23), although whether the role of *H. pylori* in the pathogenesis of rosacea is as a precipitating or exacerbating factor requires further clarification, as well as the precise mechanism of action.

A vasoactive humoral mediator, either as a flush-inducing toxin released directly from *H. pylori* (5) or as an *H. pylori*-induced gastrointestinal secretion (6, 24) has been proposed. While this might explain the role of *H. pylori* in erythemato-telangiectatic rosacea, it would fail to account for the higher prevalence observed in the

Table III. *Recent publications assessing the potential association between rosacea and Helicobacter pylori.*

Reference	Design	Number of patients	Conclusion
Rebora et al. (4, 5)	Case series	31 patients	Prevalence of histology and serology higher than expected in reference population; positive response to *H. pylori* eradication therapy
Powell et al. (6)	Case series	20 patients	*H. pylori* antibody titres higher than expected in general population
Kolibasova et al. (7)	Case report	1 patient	Marked response to *H. pylori* eradication
Utas et al. (8)	Case-control study+uncontrolled *H. pylori* eradication case series	25 cases and 87 controls; 8 patients for eradication study	No difference in seroprevalence but significant response to *H. pylori* eradication therapy
Szlachic et al. (9)	Case-control study+uncontrolled	60 cases and 60 controls;	Difference in prevalence of infection; marked response to
Szlachic (10)	*H. pylori* eradication case series	53 patients for eradication study	*H. pylori* eradication therapy
Mayr-Kanhauser et al. (11)	Case report	1 patient	Marked response to *H. pylori* eradication therapy
Schneider et al. (12)	Case-control study	94 cases and 88+14 controls	No difference in seroprevalence
Sharma et al. (13)	Case-control study	45 cases and 43 controls	No difference in seroprevalence
Jones et al. (14)	Case-control study	52 of 204 cases (serology) and 133 controls (histology+rapid urease test)	No difference in seroprevalence (cases) vs. infection prevalence (controls)
Bamford et al. (15)	Randomized, double-blind, placebo-controlled eradication trial	44 patients randomized	No difference in response between active treatment and placebo
Herr & You (16)	Case-control study+placebo-controlled *H. pylori* eradication trial	50 cases and 50 controls; 20 eradication and 20 placebo controls	No difference in infection prevalence or response to treatment
Present study	Case series	51 patients	Infection prevalence differs by severity of rosacea

papulopustular stages, unless a concomitant inflammatory mechanism, possibly localized to the facial skin by light activation, is also postulated. Interestingly, Szlachic et al. (9) reported a 72% and 65% reduction in the serum levels of the proinflammatory cytokines TNFα and IL-8, respectively, concomitant with virtually complete resolution of rosacea symptoms in patients post *H. pylori* eradication therapy.

To date, *H. pylori* has only been found colonizing the gastric mucosa. While there is no evidence that *H. pylori* colonizes the skin of the face, the higher prevalence of infection observed in this and another study (9, 10) among the inflammatory rosacea group and the successful use of a variety of topical antibiotics in the historical treatment of rosacea (25) suggest that it is prudent to investigate this possibility further.

The trend for an increasing prevalence of *H. pylori* with severity of rosacea may also provide a clue to the apparent inconsistencies observed between studies. One of the difficulties in assessing prior studies is establishing what criteria were employed in the diagnosis of rosacea. Despite the general consensus concerning the organoleptic features, in the absence of ancillary tests, the diagnosis of rosacea covers an extremely broad range of conditions, from transient erythema of hours to days duration through to extreme chronic inflammatory infiltration leading to phymata (25). If the probability of *H. pylori* infection increases with rosacea severity/inflammation, as suggested by this study, then the inclusion of either early/mild or borderline cases of rosacea will prejudice the ability to detect an *H. pylori* association by introducing a bias toward the null.

There have also been reports of rosacea showing incidental resolution in patients who have had eradication of symptomatic *H. pylori* infection (7, 8, 11). This is not particularly surprising, since rosacea is known to respond to antibiotics, and tetracyclines, erythromycin and metronidazole are recommended treatments (25). However, some authors have suggested that the range of chemically unrelated antibiotics to which rosacea responds, and in particular oral metronidazole, is of itself evidence of a common activity against *H. pylori* (26).

If *H. pylori* is important in the pathogenesis of some cases of rosacea, then one might expect eradication to produce remission. In a recent randomized controlled trial involving rosacea patients with both positive *H. pylori* serology and ^{13}C-breath tests, Bamford et al. (15) demonstrated significant improvement in rosacea severity scores in those patients treated with *H. pylori* eradication therapy, yet unexplainedly detected a similar improvement in placebo controls. In contrast, in a similar study Herr & You (16) failed to detect either a treatment or placebo effect. It is noteworthy that the greatest difference in response observed between the eradication treatment and placebo groups in both of these studies was in the reduction of number of pustular lesions on the face, which was consistently statistically significantly greater in the treatment group (15, 16). Further, Szlachic et al. (9) demonstrated marked improvement in rosacea following successful *H. pylori* eradication in over 96% (=51/53) of infected patients exhibiting papulopustular rosacea. However, if the goal is to provide amelioration of rosacea symptoms through eradication of *H. pylori* it is worth noting that the overall prevalence of concurrent *H. pylori* infection among rosacea patients was only 39% (19/49) in the current study, and was still only 46% (15/33) considering only those patients exhibiting inflammatory rosacea. Nevertheless, with respect to the population represented by the current study, we believe clinicians should possess an index of suspicion concerning *H. pylori* infection in proportion to the severity of presentation of rosacea.

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