CLINICAL REPORT

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

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Acta Derm Venereol 2003; 83: 282–286

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 13C-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; 13C-urea breath test.

(Accepted February 14, 2003.)

Acta Derm Venereol 2003; 83: 282–286.

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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 13C-urea breath test (13C-UBT – B.S.I.A. Ltd, Brentford, Middlesex, UK). The 13C-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 13C-labelled carbon dioxide produced by bacterial metabolism following a test meal containing 13C-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 kDa (Cag A) antigen of H. pylori.
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 erythematotelangiectatic versus inflammatory/papulo-pustulatular 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%...
(=15/33) of patients with inflammatory rosacea and 25.0% (=4/16) of those with only erythematotelangiectatic rosacea exhibited a positive 13C-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 13C-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 13C-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 erythematotelangiectatic 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 | Marked response to *H. pylori* eradication therapy |
| Kolhasova et al. (7) | Case-control study | 1 patient | Marked response to *H. pylori* eradication therapy |
| Utas et al. (8) | Case-control study | 8 patients for eradication study | No difference in prevalence of infections, marked response to *H. pylori* eradication therapy |
| Szlachic et al. (9) | Case-control study | 53 patients for eradication study | No difference in seroprevalence (patients) vs. infection prevalence (controls) |
| Szlachic (10) | Case-control study | 60 cases and 60 controls; 53 patients for eradication study | No difference in infection prevalence or response to treatment between active treatment and placebo |
| Schmeiser et al. (11) | Case-control study | 94 cases and 88 controls | No difference in seroprevalence |
| Sharma et al. (12) | Case-control study | 45 cases and 43 controls | No difference in seroprevalence |
| Jones et al. (13) | 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. (14) | Case-control study | 44 patients randomized | No difference in response between active treatment and placebo |
| Herr & You (15) | Case-control study | 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 |

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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 TNF-α 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 13C-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.

ACKNOWLEDGEMENT

We gratefully acknowledge Astra Pharmaceutical’s provision of breath-testing kits.

REFERENCES

1. Ryle JA, Barber HW. Gastric analysis in rosacea. Lancet 1920; ii: 1195.
2. Fry L, Swann JC. Gastrocamera studies in rosacea. Br J Dermatol 1968; 80: 737–739.
3. Marks J, Shuster S. Small intestinal mucosal abnormalities in various skin diseases: fact or fancy? Gut 1970; 11: 281–291.
4. Rebora A, Drago F, Picciotta A. Helicobacter pylori in patients with rosacea. Am J Gastroenterol 1994; 89: 1603–1604.
5. Rebora A, Drago F, Parodi A. May Helicobacter pylori be important for dermatologists? Dermatology 1995; 191: 6–8.
6. Powell FC, Daw MA, Duguid C. Positive Helicobacter pylori serology in rosacea patients. Irish J Med Sci 1993; Suppl. 161: 75.
7. Kolibasova K, Tothova I, Baumgartner J, Filo V. Eradication of Helicobacter pylori as the only successful treatment in rosacea. Arch Dermatol 1996; 132: 1393.
8. Utas S, Ozbakir O, Turasan A, Utas C. Helicobacter pylori eradication treatment reduces the severity of rosacea. J Am Acad Dermatol 1999; 40: 433–435.
9. Szlachic A, Sliwowski Z, Karczewska E, Biełanski W, Pytko-Polonczyk J, Konturek SJ. Helicobacter pylori and its eradication in rosacea. J Physiol Pharmacol 1999; 50: 777–786.
10. Szlachic A. The link between Helicobacter pylori infection and rosacea. J Eur Acad Derm Venereol 2002; 16: 328–333.
11. Mayr-Kanhauser S, Kranke B, Kaddu S, Mullegger RR. Resolution of granulomatous rosacea after eradication of Helicobacter pylori with clarithromycin, metronidazole and pantoprazole. Eur J Gastroenterol Hepatol 2001; 13: 1379–1383.
12. Schneider MA, Skinner RB, Rosenberg EW, Noah PW, Smith L, Zwarum A. Serologic determination of *Helicobacter pylori* in rosacea patients and controls. Clin Res 1992; 40: A831.

13. Sharma VK, Lynn A, Kaminski M, Vasudeva R, Howden CW. A study of the prevalence of *Helicobacter pylori* infection and other markers of upper gastrointestinal tract disease in patients with rosacea. Am J Gastroenterol 1998; 93: 220–222.

14. Jones MP, Knable AL, White MJ, Durning SJ. *Helicobacter pylori* in rosacea: lack of an association. Arch Dermatol 1998; 134: 511.

15. Bamford JTM, Tilden RL, Blankush RN, Gangeness DE. Effect of treatment of *Helicobacter pylori* infection on rosacea. Arch Dermatol 1999; 135: 659–663.

16. Herr H, You CH. Relationship between *Helicobacter pylori* and rosacea: It may be a myth. J Korean Med Sci 2000; 15: 551–554.

17. Bamford JTM. Interobserver variation in the assessment of rosacea. Arch Dermatol 1998; 134: 508.

18. Veldhuyzen van Zanten SJO, Pollak PT, Best LM, Bezanson GS, Marie T. Increasing prevalence of *Helicobacter pylori* infection with age: continuous risk of infection in adults rather than a cohort effect. J Infect Dis 1994; 169: 434–437.

19. Kosunen TU, Hook J, Rautelin HI, Myllyla G. Age-dependent increase of *Helicobacter pylori* antibodies in blood donors. Scand J Gastroenterol 1989; 24: 110–114.

20. Berg M, Lidé S. An epidemiological study of rosacea. Acta Derm Venereol 1989; 69: 419–423.

21. Logan PRH, Polson PF, Misiewicz JJ, et al. Simplified single sample 13Carbon urea breath test for *Helicobacter pylori*, comparison with histology, culture and ELISA serology. Gut 1991; 32: 1461–1464.

22. Brown KE, Peura DA. Diagnosis of *Helicobacter pylori* infection. Gastroenterol Clin North Am 1993; 22: 105–115.

23. Rothman KJ, Greenland S. Causation and causal inference. In: Rothman KJ, Greenland S, eds. Modern epidemiology. Philadelphia: Lippincott-Raven, 1998: 7–29.

24. Powell FC. Rosacea: Current concepts of pathogenesis. J Invest Dermatol 1997; 108: 94.

25. Jansen T, Plewig G. Rosacea: classification and treatment. J Roy Soc Med 1997; 90: 144–150.

26. Rebora A, Drago F. *Helicobacter pylori* and rosacea. J Am Acad Dermatol 2000; 43: 884.