CED
Clinical and Experimental Dermatology

Upper gastrointestinal findings and detection of *Helicobacter pylori* in patients with oral lichen planus

E. A. S. Attia,* N. S. A. Abdel Fattah* and H. M. Abdella**

*Departments of *Dermatology and Venereology, and **Tropical Medicine, Ain Shams University Hospitals, Cairo, Egypt*

doi:10.1111/j.1365-2230.2009.03464.x

Summary

Background. Lichen planus (LP) is a mucocutaneous disease of unknown aetiology, which may involve the gastrointestinal (GI) mucosa. The association of *Helicobacter pylori* with LP has been a subject of debate.

Aim. To investigate upper GI findings and the presence of *H. pylori* in GI mucosa and oral LP (OLP).

Methods. Oral biopsies from 20 patients with erosive OLP and 20 with non-erosive OLP were investigated for the presence of *H. pylori* by histopathological examination and PCR. Upper GI endoscopy and GI mucosal biopsies were examined for LP lesions and/or *H. pylori*.

Results. The endoscopic findings of both groups were oesophagitis, antral gastritis and duodenitis. No LP or LP-like changes were found in the upper GI mucosa. *H. pylori* was found by histopathological examination in the gastric mucosa of 18 patients (45%), with equal distribution in both the control and study groups. Positive PCR results were obtained from biopsy specimens of oral lesions in all patients with erosive OLP and presence of *H. pylori* in the stomach (9 patients), but in none of the patients with non-erosive OLP ($P = 0.001$).

Conclusion. We did not find any difference in symptoms, endoscopic findings and histopathological results between patients with erosive and non-erosive OLP. However, the concomitant presence of erosive OLP, of *H. pylori* nucleic acid in erosive OLP and the *H. pylori* organisms in gastric mucosa implies a possible pathogenic connection between this bacterium and erosive OLP.

Introduction

Lichen planus (LP) is an inflammatory disease of the skin and mucous membranes. Although the oral mucosa is commonly affected by the disease, the gastrointestinal (GI) mucosa may be also involved.[1] Early diagnosis and treatment of mucosal involvement are important because of the possibility of malignant transformation and stricture formation.[2] The exact aetiology of LP is unknown, infections and stress have been suggested as triggering factors.[3]

Helicobacter pylori is one of the most common bacteria colonizing the human GI tract, affecting nearly half of the world population.[4] In addition to its role in GI diseases, it is suggested to be associated with dermatological conditions, including LP.[5,6]

It is well established that the principal ecological niche for *H. pylori* is the gastric mucosa. Nevertheless, it is now quite certain that *H. pylori* may also be present in the oral cavity, either temporarily or permanently.[7] In addition to dental plaque and saliva, other oral sites and oral lesions are being investigated for the presence of *H. pylori* DNA, using PCR.[8,9] The aim of this study was to evaluate upper GI findings and to investigate the presence of *H. pylori* in GI mucosa and oral lesions of patients with oral LP (OLP).

Correspondence: Dr Enas Attia, Department of Dermatology and Venereology, Ain Shams University, Cairo, Egypt
E-mail: annosah74@hotmail.com

Conflict of interest: none declared.

Accepted for publication 12 February 2009

Methods

Patients

Patients with a clinical diagnosis and histopathological confirmation of OLP were selected from those attending the outpatient dermatology clinic at Ain Shams University Hospitals in the period December 2006 to February 2008. All patients underwent thorough history-taking, including oral and GI symptoms, and approximate disease duration and a thorough clinical examination with emphasis on the presence of epigastric tenderness; a dermatological examination for the presence of LP, including type, distribution, and involvement of hair and nails; and an oral examination including identification of sites of oral involvement and the clinical forms of OLP. Liver function tests (alanine and aspartate aminotransferases, serum albumin and bilirubin) were performed, and patients were tested for the presence of hepatitis C virus antibody by third-generation ELISA. Abdominal ultrasonography was also performed, to detect any abnormality that could influence the outcome of the study, such as advanced liver disease and portal hypertension. Patients without the typical histopathological features of OLP and those with concomitant diseases or medications that could affect the outcome of the study (e.g. nonpeptic dyspepsia, proton pump inhibitors) and those who had used any topical, intralesional or systemic treatment within a month before the study, were excluded.

In total, 40 patients (15 men, 25 women; mean ± SD age 51 ± 3.88 years, range 42–57 years; mean disease duration 4.45 ± 3.40 years, range 1–11) were enrolled into the study. All patients had confirmed OLP; 27 patients (67.5%) also had skin involvement, with localized distribution in 12 patients. Patients were divided into two groups according to the presence or absence of erosions: group 1 comprised 20 patients with erosive OLP and group 2 included 20 patients with non-erosive OLP (9 patients with the papular type and 11 patients with the reticular type) matched for age and gender (Table 1).

Table 1 Characteristics of the patient groups.

Characteristic	Group 1, erosive OLP (n = 20)	Group 2, non-erosive OLP (n = 20)	P
Age, years			
Mean ± SD	51.25 ± 3.64	50.75 ± 4.20	
Range	46–57	42–57	0.69
Sex n (%)			
Male	6 (30)	9 (45)	
Female	14 (70)	11 (55)	0.11
Disease duration, years			
Mean ± SD	5.6 ± 3.2	3.30 ± 3.15	
Range	(1–11)	(1–2)	0.03
Oral symptoms, n (%)			
Yes	9 (45)	4 (20)	
No	11 (55)	16 (80)	0.03
GIT symptoms, n (%)			
Yes	9 (45)	7 (35)	
No	11 (55)	13 (65)	0.21
Oral lesions, n (%)			
≤ 2	1 (5)	11 (55)	
≥ 3	19 (95)	9 (45)	0.01
Skin involvement, n (%)			
Yes	7 (35)	20 (100)	
No	13 (65)	0	0.03

OLP, oral lichen planus.

Oral biopsies

For each patient, two oral biopsies were taken from the oldest and/or severest oral lesions. The specimens were pretreated by washing in saline to improve the recovery of *H. pylori.*[10]

One biopsy specimen was fixed in formalin and embedded in paraffin wax. Sections were cut and mounted on glass slides and stained with haematoxylin and eosin for routine histopathological examination to confirm the diagnosis of OLP and to search for the presence of *H. pylori* and any dysplastic changes. The histopathological features of OLP investigated included epithelial hyperkeratosis, atrophy or hyperplasia, acanthosis, saw-tooth rete ridges, liquefaction degeneration of basal cells, single-cell keratinization, and a band-like inflammatory infiltrate dominated by lymphocytes and macrophages. The other biopsy specimen was stored in phosphate-buffered saline (PBS) at −70 °C for subsequent *H. pylori* nucleic acid extraction.

Upper gastrointestinal tract endoscopy

Patients fasted for 8 h before endoscopy. The endoscope (Pentax videoscope system; Pentax, Slough, UK) was cleaned, disinfected and rinsed before each examination. Local anaesthetic (xylocaine spray) was provided to patients. The oesophagus, stomach (fundus, body and antrum) and duodenum were examined, and biopsies were taken from several different sites: one biopsy from the lower end of oesophagus, two from each of the anterior and posterior antrum 20–50 mm from the pylorus, and two from the anterior and posterior body 100 mm from the cardia. Two additional biopsies were taken from any suspicious area found during endoscopic

examination. All endoscopic findings were reported according to the Sydney classification system.[11]

Gastrointestinal mucosa biopsies

The biopsy specimens were pretreated as described above. Two biopsy specimens from the anterior and posterior antrum were stored in PBS at −70 °C. For other biopsy specimens, the usual recommendations, derived from the Sydney system,[12] were followed. Specimens were immediately fixed in formalin. Storage in formalin was limited to preserve bacterial morphology. The specimens were correctly orientated before embedding in paraffin wax so that the sections with surface epithelium (where the bacteria are essentially located) could be identified easily. Three thin sections (3–5 μm) were cut at different levels for better observation of the surface epithelium and the crypts. All sections were stained with haematoxylin and eosin. In doubtful cases, the tissue samples stored at −70 °C were prepared for *H. pylori* detection by PCR.

Identification of *Helicobacter pylori*

The typical morphology of *H. pylori* is a comma-shaped or S-shaped bacillus (2.5–4 μm long and 0.5–1 μm thick) at high magnification. They adhere to the mucus cells or move freely within the mucus and may eventually be present in the intercellular spaces.[13]

Helicobacter pylori nucleic acid extraction and PCR amplification

Total *H. pylori* nucleic acid was extracted immediately according to the manufacturer's instructions (MagNA Pure Compact Nucleic Acid Isolation Kit; catalogue no. 03730964001; Roche Diagnostics GmBH, Mannheim, Germany), and purified in a fully automated system (MagNA Pure Compact Instrument; Roche Diagnostics). The yield of total nucleic acid obtained was determined spectrophotometrically. The primers used fpr CR were: 5′-GATAACGCTGTCGCTTCATACG-3′ and 5′-CTGCAA AAGATTGTTTGGCA-3′.

Statistical analysis

Statistical analysis was carried out using SPSS software (version 10; SPSS Inc., Chicago, IL, USA). Comparisons were performed using the unpaired *t*-test for quantitative data and the χ^2 test for qualitative data. Logistic regression analysis was used to detect any relationship between *H. pylori* in gastric mucosa and oral lesions. Significance was set at $P < 0.05$.

Results

The most characteristic clinical feature of OLP was the presence of reticular white striations and/or white papules. Papular and plaque types or erosive and ulcerative types were sometimes present.

When the two groups were compared, significant differences in disease duration and oral symptoms were found. Patients with erosive lesions had significantly longer disease duration ($P = 0.031$) and were more likely to have symptoms ($P = 0.027$). Oral symptoms included pain (most common symptom; found in 32.5% of patients), followed by burning, swelling, irritation and bleeding. Moreover, patients with erosive lesions had significantly more sites of oral involvement than did patients with reticular or papular lesions ($P = 0.011$). The buccal mucosa was the single most common site of involvement in each form (all patients, 100%), followed by the tongue (8 patients; 20%), lower lip (5 patients; 12.5%), gingivae (3 patients; 7.5%) and palate (3 patients; 7.5%). Lesions on the floor of the mouth and the upper lip were not found. No significant difference was found between the site of OLP and the clinical type of the disease. Skin involvement was present in seven patients in group 1 (five with localized distribution) and in all patients in group 2 (seven with localized distribution) and the difference was significant ($P = 0.027$).

GI symptoms included epigastric pain (most common, found in 35%), dysphagia (17.5%) and odynophagia (2.5%); there was no significant difference between the groups ($P = 0.206$). Moreover, there was no significant difference in presence of *H. pylori* in GI mucosa compared with the presence of GI symptoms or the disease duration, i.e. chronicity of OLP lesions ($P = 0.45$ and 0.27, respectively).

The results of the upper GI endoscopic examination of both groups are summarized in Table 2. The most common findings were antral gastritis (20 patients; 50%), oesophagitis (19 patients; 47.5%) and duodenitis (11 patients; 27.5%), with associated duodenal ulcer in 2 patients. Histopathological examination found evidence of chronic atrophic gastritis (25 patients; 62.5%), oesophagitis (19 patients; 47.5%), duodenitis (14 patients; 35%) and duodenal ulcer (2 patients; 5%). No LP or LP-like changes were found in any of the patients.

H. pylori was found by histopathological examination in the gastric mucosa of 18 patients (45%), with equal distribution in both groups (9 patients in each group).

Table 2 Endoscopic findings of patients with oral lichen planus.

Endoscopic findings	Group 1, erosive OLP (n = 20)	Group 2, non-erosive OLP (n = 20)
Oesophagus, *n* (%)		
Normal	7 (35)	12 (60)
Hyperaemia	0	2 (10)
Oesophagitis	7 (35)	4 (20)
Reflux oesophagitis	6 (30)	2 (10)
Stomach, *n* (%)		
Normal	9 (45)	9 (45)
Antral gastritis	9 (45)	11 (55)
Pangastritis	2 (10)	0
Ulcer	0	0
Duodenum, *n* (%)		
Normal	12 (60)	15 (75)
Duodenitis	6 (30)	5 (25)
Ulcer	2 (10)	0

OLP, oral lichen planus.

None of the 22 patients with no evidence of *H. pylori* by histopathological examination had a positive PCR result. Routine histopathological examination detected dysplasia of the oral mucosa in three patients with erosive OLP, but *H. pylori* was not found in the tissue of any of these three patients even after sectioning several times. However, all patients with erosive OLP and evidence of *H. pylori* in the stomach (9 patients) had positive PCR results for *H. pylori* in oral lesions whereas none of the patients in group 2 without evidence of *H. pylori* in the stomach (9 patients) had positive PCR results for *H. pylori* (Table 3); the difference was highly significant (P = 0.001). Using regression analysis, a highly significant relationship was found between the presence of *H. pylori* in the gastric mucosa and its detection by PCR in erosive OLP lesions (P = 0.001).

Discussion

In our study, dysplasia of the oral lesions was present in three patients with erosive OLP (15%). This highlights the importance of histopathological evaluation and continuous follow-up of such cases for the possibility of malignant transformation. Controversies surround this issue in the literature, as the reported frequency ranges from 0% to 5.3%.[14,15] Therefore, the potential of malignant transformation in OLP and the type of OLP that should be considered premalignant remains to be elucidated.

Table 3 Prevalence of *Helicobacter pylori* in erosive and non-erosive oral lichen planus.

Detection method	Endoscopic findings: Both groups	Endoscopic findings: Group 1, erosive OLP (n = 20)
H&E (gastric mucosa), *n* (%)	9 (45)	9 (45)
H&E (OLP), *n* (%)	Absent (0)	Absent (0)
PCR (OLP), *n* (%)	9 (45)	Absent (0)

H&E, haematoxylin and eosin; OLP, oral lichen planus.

GI symptoms were present in 16 of our patients (40%), including epigastric pain (the most common), dysphagia and odynophagia. Sanli *et al.*[1] reported GI symptoms in four cases (20%), with hunger pain in three patients, dysphagia in one and flatus in one. The discrepancy between our findings and theirs could be attributed to our exclusion of patients with GI or abdominal diseases that could present with similar symptoms, such as gall bladder and advanced liver diseases. The exclusion criteria of Sanli *et al.* were not explicit and thus, the reported hunger pains and flatus in their patients may have been due to associated abdominal diseases.

Previous studies have shown involvement of the GI mucosa, especially the oesophagus, in patients with LP.[16] On upper GI endoscopic examination, we found antral gastritis, oesophagitis and duodenitis in our patients. Sanli *et al.* reported that the most common findings on endoscopy were antral gastritis (35%), oesophagitis (20%) and bulbitis (15%), and histopathological examination correspondingly detected chronic atrophic gastritis (45%), oesophagitis (35%), bulbitis (10%) and erosive gastritis (5%). Those authors also detected oesophageal LP-like changes in one patient (5%).[1] We found no evidence of LP or LP-like lesions in our patients, either by upper GI endoscopy or histopathological examination of biopsies taken from different sites. In contrast, Dickens *et al.*[16] found oesophageal lesions in 5 of 19 patients with LP on endoscopy (erosive lesions in 1 and papular lesions in 4). However, confirmation of their results by histopathological examination of biopsy specimens of the oesophageal mucosa lesions was not possible due to acid reflux in their patients.

The results of our study did not reveal any difference in GI symptoms, endoscopic findings and histopathological examination between patients with erosive and non-erosive OLP. These findings could not be compared with other studies, due to the absence of comparative studies of these issues in the different forms of OLP.

We chose to investigate a possible role of *H pylori* in patients with LP for several reasons. First, the exact aetiology of LP is not fully understood, although infections and stress are suspected triggering factors.[3]

Second, it is a mucocutaneous disease, with possibility of erosion or ulcer formation, and another stress-related ulcerative disease, peptic ulcer, is closely connected with *H. pylori* infection.[9] Third, it is one of the dermatological conditions under debate regarding its association with *H. pylori.*[6] Moravvej *et al.* support a definite aetiological role for *H. pylori* in LP through their case–control study, which found a significantly higher frequency of *H. pylori* in cases, using the urea breath test.[6]

However, some controversial reports have been published regarding the beneficial effects of *H. pylori* eradication in patients with LP. Daudén *et al.*[17] found almost equal prevalence of *H. pylori* in patients with LP and controls, using the urea breath test. When *H. pylori* eradication therapy was given to 15 patients, successful eradication was achieved in 10, but the LP lesions had only partial remission in 3, were unchanged in 4 and were aggravated in 3 patients. In contrast, Vainio *et al.*[3] found a beneficial effect of eradication. They studied peptic ulcer and *H. pylori* in 78 patients with LP, using serum IgG antibodies to *H. pylori.* They found a significantly higher frequency of history of peptic ulcer in patients with chronic or recurring LP than in patients with transient LP, controls and the general Finnish population (28%, 8%, 10.5% and 5.9%, respectively). Moreover, *H. pylori* infection was present in 66% of patients with chronic/repeating LP, indicating that eradication therapy should be considered in those patients.

Worldwide, *H. pylori* represents the most common infection in humans, affecting nearly 50% of the world population.[4] In accordance with the established worldwide rate of prevalence, we found histopathological evidence of *H. pylori* infection in the gastric mucosa of 18 of our patients (45%), with equal distribution in both groups. None of the 22 patients without histopathological evidence of *H. pylori* had positive PCR results, confirming that histological detection of *H. pylori* in the GI mucosa can reach a high sensitivity (95%) under optimum conditions.[13]

Previous studies on Egyptian patients found that 86.4% of patients with nonulcer dyspepsia were positive for *H. pylori,* using the rapid urease test.[18] Using serological tests, Salem *et al.*[19] also found an overall prevalence of 87.6% among asymptomatic patients. Thus, further studies on larger groups of patients are needed to establish an accurate prevalence rate of *H. pylori* infection among Egyptians.

Although *H. pylori* bacteria colonize the stomach and the upper part of the duodenum, their natural reservoir is unconfirmed. Much attention has been directed to the possible role of the oral cavity. Moreover, the histological similarities between gastric and oral ulcers may assume possible involvement of *H. pylori* in the development of ulcerative oral lesions.[9]

In the present study, we found no evidence of *H. pylori* in OLP lesions by routine histopathological examination, but PCR gave positive results for all patients with erosive OLP and confirmation of *H. pylori* presence in the stomach; in contrast, none of the patients with non-erosive OLP had positive *H. pylori* tests, either by histopathology or PCR. A highly significant relationship was found between the presence of *H. pylori* in the gastric mucosa and its detection in erosive OLP lesions, denoting a potential role of this bacterium in erosive OLP, although the possibility of it being a secondary invader cannot be excluded.

Regarding the contribution that *H. pylori* plays in the pathogenesis of extra-gastric diseases, the exact role is not yet clear and speculations include direct as well as indirect mechanisms.[6,20,21] Modulation of immunological processes that may involve the skin have been described.[22] *H. pylori* toxins can act as superantigens and thus mediate inflammatory skin lesions. Therefore, further studies investigating the expression of *H. pylori* toxins have been recommended to clarify the role of *H. pylori* in skin diseases.[23]

Several important questions remain to be answered. Are the positive PCR results for *H. pylori* in erosive LP in patients with *H. pylori* in their stomachs the result of a breach in the oral mucosa? Does *H. pylori* infection play a role in erosive OLP and does its eradication represent a beneficial effect or modify the disease outcome, or is the bacterium merely a secondary invader of the erosions present in OLP? Another important question is whether the oral and gastric mucosae are infected by the same strains of *H. pylori*. Blaser and Berg proposed that *H. pylori* a is highly mutable bacterium, capable of rapid exchange of its genetic material from one strain to another, depending on the environmental conditions present in the numerous different local niches in the oral cavity.[24]

In conclusion, our study did not reveal any differences in GI symptoms, endoscopic findings and histopathological results between patients with erosive and non-erosive OLP. However, the concomitant presence of erosive OLP, *H. pylori* nucleic acid in erosive oral lesions, and *H. pylori* in gastric mucosa suggests a possible pathogenic connection between this bacterial infection and erosive OLP. However, caution must be taken not to implicate this bacterium as the infectious agent responsible for every case of erosive OLP with *H. pylori* gastric disease, particularly because *H. pylori* infection is very common, thus the possibility of it being

a secondary invader cannot be excluded. Additional large-scale studies including adequate diagnostic schedules, sufficient eradication treatment protocols, confirmation of eradication and adequate control groups are warranted.

Acknowledgements

We thank the members of the Oral Medicine Department, Faculty of Dentistry and Pathology Department, Faculty of Medicine, Ain Shams University, for their cooperation and assistance. Extended special thanks go to Finan Specialized Gene Tech Centre, Cairo, Egypt, for technical support.

References

1 Sanli H, Cetinkaya H, Tursen U *et al.* Upper gastrointestinal findings in oral lichen planus. *Turk J Gastroenterol* 2002; **13**: 31–4.
2 Sigurgeirsson B, Lindelof B. Lichen planus and malignancy: an epidemiologic study of 2071 patients and a review of literature. *Arch Dermatol* 1991; **127**: 1684–8.
3 Vainio E, Huovinen S, Liutu M *et al.* Peptic ulcer and Helicobacter pylori in patients with lichen planus. *Acta Derm Venereol* 2000; **80**: 427–9.
4 Moravvej H, Hoseini H, Barikbin B *et al.* Association of Helicobacter pylori with lichen planus. *Indian J Dermatol* 2007; **52**: 138–40.
5 Malekzadeh R, Mohamadnejad M, Siavoshi F *et al.* Treatment of Helicobacter pylori infection in Iran: low efficacy of recommended western regimens. *Arch Iranian Med* 2004; **7**: 1–19.
6 Nilsson HO, Pietroiusti A, Gabrielli M *et al.* Helicobacter pylori and extragastric diseases – other Helicobacter. *Helicobacter* 2005; **10**: 54–65.
7 Loster BW, Majewski SW, Czesnikiewicz-Guzik M *et al.* The relationship between the presence of Helicobacter pylori in the oral cavity and gastric in the stomach. *J Physiol Pharmacol* 2006; **57**: 91–100.
8 Maravak-Stipetic M, Gall-Trošelj K, Lukac J *et al.* Detection of Helicobacter pylori in various oral lesions by nested polymerase chain reaction (PCR). *J Oral Pathol Med* 1988; **27**: 1–3.
9 Riggio MP, Lennon A, Wray D. Detection of Helicobacter pylori DNA in recurrent aphthous stomatitis tissue by PCR. *J Oral Pathol Med* 2000; **29**: 507–13.
10 Jonkers D, Stobberingh E, Stockbrugger R. Influence of oropharyngeal flora and specimen pretreatment on the recovery of Helicobacter pylori. *Eur J Clin Microbiol Infect Dis* 1996; **15**: 378–82.
11 Tytgat G. The Sydney system: endoscopic division, endoscopic appearance in gastritis-duodenitis. *J Gastroentrol Hepatol* 1991; **6**: 223–34.
12 Price AB. The Sydney System: histological division. *J Gastroenterol Hepatol* 1991; **6**: 209–22.
13 Me'graud F, Lehours P. Helicobacter pylori detection and antimicrobial susceptibility testing. *Clin Microbiol Rev* 2007; **20**: 280–322.
14 Ismail SB, Kumar SKS, Zain RB. Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management, and malignant transformation. *J Oral Sci* 2007; **49**: 89–106.
15 Gonzalez Moles MA, Scully C. Oral lichen planus: controversies surrounding malignant transformation. *Oral Dis* 2008; **14**: 229–43.
16 Dickens CM, Heseltine D, Walton S *et al.* The esophagus in lichen planus: an endoscopic study. *BMJ* 1990; **300**: 84.
17 Daudén E, Vasquez-Carrasco MA, Penas PF *et al.* Association of Helicobacter pylori infection with psoriasis and lichen planus: prevalence and effect of eradication therapy. *Arch Dermatol* 2000; **136**: 1275–6.
18 El-Zayadi A, El-Wakil MR, El-Okby SG. The use of rapid urease test in diagnosis of Helicobacter pylori among~non ulcer dyspepsia patients in Egypt. *Journal of Tropical Medicine* 1990; **1**: 55.
19 Salem DE, Yousri A, Farag H. The prevalence of H. pylori antibodies in young Egyptian asymptomatic persons. *Presented at the Annual Meeting of Egyptian Society of gastroenterology and Egyptian Society of Ultrasonography, Cairo, 1992.*
20 Gasbarrini A, Franceschi F, Armuzzi A *et al.* Extradigestive manifestations of Helicobacter pylori gastric infection. *Gut* 1999; **45**: I9–12.
21 Negrini R, Savio A, Poiesi C *et al.* Antigenic mimicry between Helicobacter pylori and gastric mucosa in the pathogenesis of body atrophic gastritis. *Gastroenterology* 1996; **111**: 655–65.
22 Engstrand L, Gustavsson S, Schwan A *et al.* Local and systemic immune response in Helicobacter pylori-associated chronic gastritis before and after treatment. *Scand J Gastroenterol* 1993; **28**: 1105–11.
23 Leung DYM, Hauk P, Strickland I *et al.* The role of superantigens in human diseases: therapeutic implications for the treatment of skin diseases. *Br J Dermatol* 1998; **139**: 17–29.
24 Blaser MJ, Berg DE. Helicobacter pylori genetic diversity and risk of human disease. *J Clin Invest* 2001; **107**: 767–73.