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Clinical Study

Helicobacter pylori Infection and Light Chain Gammopathy

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Objective. Helicobacter pylori provokes a host of immune alterations upon colonizing the gastric mucosa. Design. We report 22 individuals with confirmed Helicobacter pylori infection who were also managed for the concurrent elevation of immunoglobulin free light chain (kappa and lambda) levels. Result. Of the 22 patients, 15 patients (68.2%) had elevated free light chain levels: 6 patients (40%) had only kappa chain elevation, 2 patients (13.3%) had only lambda chain elevation, and 7 patients (46.7%) had both kappa and lambda chain elevation. Twenty out of the 22 patients (90.9%) were microbiologically confirmed cured with 3 patients being lost to follow-up for repeat levels. Of the 3 patients who were lost to follow-up, 1 patient had only kappa chain elevation, 1 patient had only lambda chain elevation, and 1 patient had both kappa and lambda chain elevation. For those who were cured (19 patients), 5 patients with kappa elevation had normalized values, 4 patients with lambda elevation had normalized values, and 2 patients with combined kappa and lambda elevation had normalized values. For 6 out of the 19 patients, the light chain levels remained elevated. Conclusion. We speculate that the Helicobacter pylori infection disrupts the immunoglobulin system with potential implications being discussed below.

1. Introduction

Helicobacter pylori is one of the most pervasive bacterial pathogens worldwide and is associated with an increased risk of gastritis, gastric and duodenal ulcers, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma [1, 2]. Indeed, it has been nearly three decades since the Australian physicians Warren and Marshall first isolated the pathogen and elucidated its association with gastric and duodenal ulcers as well as gastritis, leading to significant research towards the treatment of these gastrointestinal disorders [3]. While the incidence of the H. pylori infection varies largely by socioeconomic status, geographic region, age, and race, approximately one-half of the world’s population has been estimated to be infected, with the prevalence ranging from 30 to 40 percent in the United States [4, 5]. In fact, in the United States, the prevalence increases from less than 20% at 20 years of age to nearly 50% at 50 years of age [6]. Today, with the advent of the newer concomitant quadruple therapy, the eradication of H. pylori has experienced success rates greater than 90 percent [7, 8].

In a patient with light chain deposition disease, a transient increase in light chain levels was observed upon H. pylori infection; while levels did not normalize after microbiological cure, they down trended and returned to the patient’s baseline. The aforementioned phenomenon led us to evaluate if there was in fact a disruption in the immunoglobulin system, specifically in regards to free light chains, that accompanies the Helicobacter pylori infection (J. Girón, personal observation).

2. Methods

In total, twenty-two adult patients—7 female patients and 15 male patients—who were diagnosed and selected randomly with H. pylori disease from 2009 to 2011, confirmed by a positive stool antigen test via an enzyme immunoassay
Table 1: Patient demographics.

| Characteristic             | Result |
|----------------------------|--------|
| Total patients             | 22     |
| Sex, %                     |        |
| Men                        | 31.8   |
| Women                      | 68.2   |
| Age (mean), years          | 51.9   |
| Age (range), years         | 30–85  |
| Confirmed *H. Pylori* microbiologic cure*, % | 90.9%  |

* A microbiological cure was confirmed by a positive stool antigen test via an enzyme immunoassay by the laboratories at Quest or LabCorp.

(H. pylori), had a quantitative evaluation of free kappa and lambda light chain levels in serum (Table 1). The noninvasive *H. pylori* stool antigen test that was utilized has an overall sensitivity of 91% and specificity of 93% [9]. All of the patients were subject to a thorough history and clinical examination in addition to a complete laboratory investigation to determine their *H. pylori* status as well as the presence of other potential infectious diseases.

The patients typically received a 7-to-10 day oral regimen of clarithromycin, metronidazole, omeprazole, and bismuth subsalicylate (Table 3). All of the patients with hepatitis C, except patient 19, received *Helicobacter pylori* treatment prior to the institution of treatment for hepatitis C. Thus, changes in light chain levels were recorded before the patients were treated for hepatitis C. Patient 19 received treatment for strongyloidiasis but did not adhere to treatment for *H. pylori* or hepatitis C (Table 4(c)). Confirmation of a microbiological cure of the *H. pylori* infection with a repeat stool antigen test was performed along with a repeat measurement of the free light chain levels if previously elevated. All patients were informed of the additional blood testing. Confirmatory testing was performed from 3 weeks to 130 weeks after the completion of treatment. The associated comorbid conditions were also recorded (Table 2).

3. Results

The study included 22 patients with ages ranging from 30 to 85 years (mean of 51.9 years of age) (Table 1). Fifteen patients had confirmed *H. pylori* disease and elevated light chain levels. For 6 out of 15 patients (40%), only elevated free kappa light chain levels were found, and for 2 out of 15 patients (13.3%), only elevated free lambda light chain levels were found. For 7 out of 15 patients (46.7%), both kappa and lambda light chain elevation was found. Overall, 15 out of the 22 patients (68.2%) had an elevation in free kappa and/or lambda light chain levels (Tables 2 and 3), while 7 patients (31.8%) had normal lambda and kappa light chain levels.

Twenty of the twenty-two patients (90.9%) were confirmed microbiologically cured of the *H. pylori* infection as evidenced by a repeat stool antigen test (Table 1). Three patients (13.6%) failed to follow-up in an outpatient setting to repeat free light chain values. Out of the 3 patients who were lost to follow-up for repeat light chain values, 1 patient had only kappa chain elevation, 1 patient had only lambda chain elevation, and 1 patient had both kappa and lambda chain elevation.

We had 15 patients with confirmed *H. pylori* eradication and abnormal light chain levels. Light chain levels were monitored over a period of 3 to 130 weeks. Of these 15 patients, 3 patients were lost to follow-up (Table 4(d)). Three patients with solitary kappa light chain elevation experienced...
Table 4: Tracking free kappa and lambda light chain values in *H. pylori* patients.

(a) Patients with initial normal kappa and lambda light chain levels

| Patient | Age | Sex  | Comorbid diseases                              | Time for confirmation of microbiological cure (weeks) | Initial $\kappa$ value (mg/L) | Initial $\lambda$ value (mg/L) |
|---------|-----|------|------------------------------------------------|-----------------------------------------------------|-----------------------------|-------------------------------|
| 1       | 30  | Female | Hepatitis B                                  | 8.1                                                  | 13.8 (N)                      | 13.3 (N)                     |
| 2       | 43  | Female | None                                          | 4.9                                                  | 11.7 (N)                      | 12.9 (N)                     |
| 3       | 48  | Male   | Human immunodeficiency virus, *Strongyloides stercoralis*, *Treponema pallidum* | 10.3                                                  | 15.23 (N)                    | 12.36 (N)                    |
| 4       | 49  | Male   | Hepatitis C                                  | 6.3                                                  | 10.6 (N)                      | 14.4 (N)                     |
| 5       | 52  | Female | Hepatitis B                                  | 11.1                                                 | 17 (N)                       | 24.7 (N)                     |
| 6       | 57  | Male   | Hepatitis C                                  | 20.7                                                 | 15.2 (N)                      | 16.2 (N)                     |
| 7       | 59  | Female | *Strongyloides stercoralis*, Schistosomiasis  | 14.1                                                 | 11.7 (N)                      | 12.6 (N)                     |

(b) Patients with elevated kappa and/or lambda light chain levels who experienced normalization of values

| Patient | Age | Sex  | Comorbid diseases                              | Time for confirmation of microbiological Cure (weeks) | Initial $\kappa$ value (mg/L) | Final $\kappa$ value (mg/L) | Normalization of $\kappa$ value | Time span between initial and final light chain value (weeks) |
|---------|-----|------|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------------|-------------------------------|---------------------------------------------------------------|
| 8       | 32  | Female | Hepatitis B, Acquired immunodeficiency syndrome, human T-lymphotropic virus-I/II, erythrasma | 2                                                   | 20.2 (A)                      | 16.78 (N)                   | Yes                           | N/A                           |
| 9       | 42  | Male   | Hepatitis C                                    | 14                                                  | 19.1 (N)                      | 10 (N)                      | N/A                           | 23.6                          |
| 10      | 50  | Male   | Methicillin-resistant *Staphylococcus aureus*, type 2 diabetes mellitus | 4.6                                                  | 19.7 (A)                      | 16.02 (N)                   | Yes                           | 3.1                           |
| 11      | 52  | Male   | Sarcoidosis, idiopathic CD4+ lymphocytopenia, erythema nodosum, hypertension *Treponema pallidum*, type 2 diabetes mellitus | 129.4                                                | 271 (A)                      | 17.4 (N)                    | Yes                           | 129.4                         |
| 12      | 54  | Female | Treponema pallidum, type 2 diabetes mellitus, hyperlipidemia, hypertension | 4.7                                                  | 28.7 (A)                      | 15.2 (N)                    | Yes                           | 4.7                           |
| 13      | 55  | Male   | Treponema pallidum, type 2 diabetes mellitus, hyperlipidemia, hypertension | 12.6                                                 | 22.1 (A)                      | 17.9 (N)                    | Yes                           | 12.6                           |

Patient 8 has a chronic carrier state of hepatitis B surface antigen and a negative viral load. This patient has not received treatment for hepatitis B.

Patient 9 is on HIV medications and had light chain values normalized with *H. pylori* treatment.

Patient 10 received treatment for *H. pylori* prior to institution of hepatitis C treatment.

Patient 11 had a methicillin-resistant *Staphylococcus aureus* infection treated with persistently elevated light chain levels that are subsequently normalized after treatment of *H. pylori*.

Patient 13 received treatment for *H. pylori* prior to institution of syphilis treatment.
(c) Patients with elevated kappa and/or lambda light chain levels who experienced persistent elevation of values

| Patient Age | Sex  | Comorbid diseases                                                                 | Time for confirmation of microbiological cure (weeks) | Initial $\kappa$ value (mg/L) | Final $\kappa$ value (mg/L) | Normalization of $\kappa$ value | Initial $\lambda$ value (mg/L) | Final $\lambda$ value (mg/L) | Normalization of $\lambda$ value | Time span between initial and final light chain value (weeks) |
|------------|------|----------------------------------------------------------------------------------|-----------------------------------------------------|-------------------------------|-----------------------------|-------------------------------|-------------------------------|-----------------------------|-------------------------------|---------------------------------------------------------------|
| 14         | 47   | Male, Acquired immunodeficiency syndrome, Hepatitis C, *Chlamydia pneumoniae*    | 5.9                                                 | 34.4 (A)                      | 43 (A)                      | No                            | 49.2 (A)                      | 56.2 (A)                      | No                            | 5.1                                           |
| 15         | 52   | Male, Hepatitis C, Chlamydia pneumoniae                                           | 10.6                                                | 30.22 (A)                     | 44.74 (A)                   | No                            | 26.73 (A)                     | 27.07 (A)                     | No                            | 7.1                                           |
| 16         | 64   | Female, Acquired immunodeficiency syndrome, Hepatitis C, glucose-6-phosphate dehydrogenase deficiency, Strongyloides stercoralis | 11.7                                                | 22.9 (A)                      | 23.1 (A)                    | No                            | 12.3 (N)                      | 11.7 (N)                      | N/A                           | 4.3                                           |
| 17         | 51   | Male, Hepatitis C, Hypertension, Hepatitis C, Strongyloides stercoralis, type 2 diabetes mellitus | 34.3                                                | 24 (A)                        | 20.8 (A)                    | No                            | 30 (A)                        | 23.6 (N)                      | Yes                           | 51.3                                          |
| 18         | 54   | Male, Hepatitis C, Hypertension, Hepatitis C, Strongyloides stercoralis, type 2 diabetes mellitus | 10.7                                                | 21.43 (A)                     | 41.74 (A)                   | No                            | 31.26 (A)                     | 71.23 (A)                     | No                            | 11.7                                          |
| 19         | 71   | Male, Polymyalgia rheumatica, coronary artery disease                             | 4.3                                                 | 25.5 (A)                      | 29.1 (A)                    | No                            | 20.7 (N)                      | 21.1 (N)                      | N/A                           | 2.7                                           |

Patients 15, 16, and 18 who have hepatic C received treatment for *H. pylori* prior to initiation of hepatitis C treatment. Patient 19 did not receive treatment for *H. pylori* and is awaiting further workup for hepatitis C.

(d) Patients who were lost to follow-up for repeat light chain values

| Patient Age | Sex  | Comorbid diseases                                                                 | Time for confirmation of microbiological cure (weeks) | Initial $\kappa$ value (mg/L) | Final $\kappa$ value (mg/L) | Normalization of $\kappa$ value | Initial $\lambda$ value (mg/L) | Final $\lambda$ value (mg/L) | Normalization of $\lambda$ value | Time span between initial and final light chain value (weeks) |
|------------|------|----------------------------------------------------------------------------------|-----------------------------------------------------|-------------------------------|-----------------------------|-------------------------------|-------------------------------|-----------------------------|-------------------------------|---------------------------------------------------------------|
| 20         | 46   | Male, Chlamydia pneumoniae, human immunodeficiency virus                          | 8.1                                                 | 340 (A)                       | Not measured                | N/A                           | 195 (A)                       | Not measured                | N/A                           | N/A                                           |
| 21         | 48   | Male, Acquired immunodeficiency syndrome                                          | Unknown                                             | 18 (N)                        | Not measured                | N/A                           | 29.55 (A)                     | Not measured                | N/A                           | N/A                                           |
| 22         | 85   | Male, Polymyalgia rheumatica, coronary artery disease                             | Unknown                                             | 25.2 (A)                      | Not measured                | N/A                           | 25.6 (N)                      | Not measured                | N/A                           | N/A                                           |
normalization of levels. One patient with solitary lambda light chain elevation experienced normalization of levels. Finally, 2 patients with combined kappa and lambda light chain elevation experienced normalization of both levels (Tables 4(a), 4(b), and 4(c)). The remaining 6 patients had persistent elevation of kappa and/or lambda light chain levels after successful eradication of *H. pylori* (Table 4(c)).

We had 7 patients with hepatitis C and *H. pylori* infection. In 5 patients tested for cryoglobulins, all 5 were negative.

### 4. Discussion

To our knowledge, this is the first observation of an association between *Helicobacter pylori* infection and an elevation of immunoglobulin free light chains. We found that 15 out of 22 patients (68.2%) had at least one light chain elevated at the time of *H. pylori* diagnosis, while 7 out of 22 (31.8%) patients had no disturbance in light chain levels. Our study has not investigated the cause of this phenomenon. We speculate that either unique bacterial strain factors, a host genetic difference among patients, or a combination of both might account for our observations. Some strains of *H. pylori* have been identified as having low virulence and fail to incite any gastroduodenal disease. Certain hosts carry a particular HLA-DQA gene which induces a potent *H. pylori* antibodies and T-cell response [10–13]. Our findings raise the possibility of stratifying *H. pylori* patients into those with abnormal light chain levels and those with normal levels. Long term follow-up of patients with persistent elevation of light chain levels may lead to a better understanding of the biologic processes involved.

A few reports of Russell body gastritis in *H. pylori* patients show light chain deposits in the tissues of the gastric mucosa and raise an intriguing notion as to a possible unique immunologic defense mechanism or immune disruption occurring in *H. pylori* infected tissue [14–16]. For example, while *H. pylori* ’s urease activity is vital for its survival, an enhanced immunological response to the enzyme may decrease the bacteria’s persistence and sequelae [17]. The gene products of cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) are associated with a robust production of cytokines and tissue inflammation [18, 19]. The presence or absence of the aforementioned proteins assists in classifying the distinct strains of *H. pylori* as well as providing further information as to its association with disease [20]. The virulent cag pathogenicity island (PAI), which encodes the bacterial oncoprotein CagA, has been strongly linked to carcinogenesis and is found in nearly 70% of *H. pylori* strains worldwide [21, 22]. The connection between *H. pylori* and disease may lie in the epigenetic control of gene expression as the CagA protein not only interferes with the host’s cytoskeleton and cell-signaling pathways but also reduces levels of p53 expression and increases the persistence of damaged DNA [23, 24]. Furthermore, the CagA protein has been shown to disrupt typical epithelial differentiation similar to the process of epithelial-to-mesenchymal transition (EMT) and is thought to play a role in tumorigenesis [25]. Thus, it has been theorized that gastric carcinomas can be mediated by *Helicobacter pylori*’s dynamic inflammatory effects on the p53 tumor suppressor gene, which has been found in 38–71% of gastric neoplasms [26, 27]. Certainly, further investigation of the gastric and intestinal flora along with the epigenetic influence of cagPAI may provide insight into how *Helicobacter pylori* is influenced by its gastrointestinal environment and can incite immune-mediated disease in patients [28].

Terrier et al. (2009) have reported elevated immunoglobulin light chain levels in patients with hepatitis C infection and mixed cryoglobulinemia [29]. In this series, 5 of the 7 patients with hepatitis C in whom cryoglobulin levels were tested had negative values, suggesting that the elevation of light chain levels was not associated with cryoglobulinemia. Except patient 19, all of the patients with hepatitis C and *Helicobacter pylori* coinfection received treatment for *H. pylori* prior to the initiation of hepatitis C therapy. Patient 19 failed to take the *H. pylori* medication and has not been treated for hepatitis C. In patient 10, normalization of light chain levels after *H. pylori* treatment and prior to initiation of hepatitis C treatment suggests that the initial light chain elevation was a result of the *H. pylori* infection. The persistence of elevated light chain levels in patients 15, 16, and 18 after *H. pylori* treatment and before hepatitis C treatment raises the possibility that hepatitis C may have contributed to this immune disturbance. Further studies will need to be conducted to further investigate this issue.

The persistence of light chain elevation in 6 out of the 19 patients suggests an ongoing stimulus of the immunoglobulin system which might be the result of either a coinfection with hepatitis C or another comorbid process. Alternatively, in the individuals with persistently elevated light chain levels, the prior infection with *Helicobacter pylori* may have initiated the early stage of a light chain immunoglobulin dysfunction. This potential immunoglobulin system dysfunction may represent the first stage in the development of a monoclonal gamopathy of unknown significance (MGUS), as the stomach, intestines, and associated lymphoid tissues constitute the largest immune organ in the human body, such a hypothesis is worth exploring.

### 5. Summary

(i) What is already known about this subject is as follows.

(i) The prevalence of *H. pylori* ranges from 30 to 40 percent in the United States.

(ii) *H. pylori* is associated with gastric and duodenal ulcers, gastric adenocarcinoma, and MALT lymphoma.

(iii) Reports of Russell body gastritis in *H. pylori* patients show light chain deposits.

(ii) The new findings are as follows.

(i) This is the first observation of association between *Helicobacter pylori* and an elevation of immunoglobulin free light chains.

(ii) 15/22 patients (68.2%) had at least one light chain elevated during *H. pylori* diagnosis.
(iii) Persistence of light chain elevation in 6/19 patients (31.6%) suggests ongoing stimulus of immunoglobulin system.

(3) How it might impact on clinical practice in foreseeable future is as follows:

(i) give possibility of stratifying H. pylori patients into those with abnormal light chain levels and those with normal levels;

(ii) allow clinicians to track patients with persistently elevated light chain levels in what may represent the first stage in the development of a monoclonal gammopathy of unknown significance (MGUS);

(iii) suggest long term follow-up on patients with persistent elevation of light chain levels for a better understanding of the biologic processes involved.

Conflict of Interests
The authors declare that there is no conflict of interests regarding the publication of this paper.

Disclosure
Dr. José Girón is the guarantor of the paper.

Authors’ Contribution
Dr. José Girón conceptualized the study, while Dr. Shawn Shah collected and statistically evaluated the data. Dr. Girón and Dr. Shah drafted the paper together, and have approved the final draft that has been submitted.

References
[1] W. D. Chey and B. C. Y. Wong, "American College of Gastroenterology guideline on the management of Helicobacter pylori infection," American Journal of Gastroenterology, vol. 102, no. 8, pp. 1808–1825, 2007.
[2] T. L. Cover and M. J. Blaser, "Helicobacter pylori in health and disease," Gastroenterology, vol. 136, no. 6, pp. 1863–1873, 2009.
[3] B. J. Marshall and J. R. Warren, "Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration," The lancet, vol. 1, no. 8390, pp. 1311–1315, 1984.
[4] R. Menon, A. Riera, and A. Ahmad, "A global perspective on gastrointestinal diseases," Gastroenterology Clinics of North America, vol. 40, no. 2, pp. 427–439, 2011.
[5] J. G. Smith, W. Li, and R. S. Rosson, "Prevalence, clinical and endoscopic predictors of Helicobacter pylori infection in an urban population," Connecticut Medicine, vol. 73, no. 3, pp. 133–137, 2009.
[6] C. P. Dooley, H. Cohen, P. L. Fitzgibbons et al., "Prevalence of Helicobacter pylori infection and histologic gastritis in asymptomatic persons," The New England Journal of Medicine, vol. 321, no. 23, pp. 1562–1566, 1989.
[7] D. C. Wu, P. I. Hsu et al., "Sequential and concomitant therapy with four drugs is equally effective for eradication of H. pylori infection," Clinical Gastroenterology and Hepatology, vol. 8, no. 1, pp. 36.e1–41.e1, 2010.
[8] A. Zullo, V. De Francesco, C. Hassan, S. Morini, and D. Vaira, "The sequential therapy regimen for Helicobacter pylori eradication: a pooled-data analysis," Gut, vol. 56, no. 10, pp. 1353–1357, 2007.
[9] J. P. Gisbert and J. M. Pajares, "Stool antigen test for the diagnosis of Helicobacter pylori infection: a systematic review," Helicobacter, vol. 9, no. 4, pp. 347–368, 2004.
[10] T. Azuma, J. Konishi, Y. Tanaka et al., "Contribution of HLA-DQA gene to host’s response against Helicobacter pylori," The Lancet, vol. 343, no. 8896, pp. 542–543, 1994.
[11] C. K. Lee, R. Weltzin, W. D. Thomas Jr. et al., "Oral immunization with recombinant Helicobacter pylori urease induces secretory IgA antibodies and protects mice from challenge with Helicobacter felis," Journal of Infectious Diseases, vol. 172, no. 1, pp. 161–172, 1995.
[12] M. Marchetti, B. Arico, D. Burroni, N. Figura, R. Rappuoli, and P. Ghiara, "Development of a mouse model of Helicobacter pylori infection that mimics human disease," Science, vol. 267, no. 5204, pp. 1655–1658, 1995.
[13] M. M. D’Elia, M. Manghetti, F. Almerigogna et al., "Different cytokine profile and antigen-specificity repertoire in Helicobacter pylori-specific T cell clones from the antrum of chronic gastritis patients with or without peptic ulcer," European Journal of Immunology, vol. 27, no. 7, pp. 1751–1755, 1997.
[14] S. Licci, P. Sette, F. Del Normo, S. Ciarletti, A. Antinort, and L. Morelli, "Russell body gastritis associated with Helicobacter pylori Infection in an HIV-positive patient: case report and review of the literature," Zeitschrift fur Gastroenterologie, vol. 47, no. 4, pp. 357–360, 2009.
[15] S. Paik, S.-I. Kim, J.-H. Kim, W. I. Yang, and Y. C. Lee, "Russell body gastritis associated with Helicobacter pylori infection: a case report," Journal of Clinical Pathology, vol. 59, no. 12, pp. 1316–1319, 2006.
[16] A. Ensari, B. Savas, A. O. Heper, I. Kuzu, and R. Idilman, "An unusual presentation of Helicobacter pylori infection: so-called ‘Russell body gastritis’," Virchows Archiv, vol. 446, no. 4, pp. 463–466, 2005.
[17] Y. Leal-Herrera, J. Torres, G. Perez-Perez et al., "Serologic IgG response to urease in Helicobacter pylori-infected persons from Mexico," American Journal of Tropical Medicine and Hygiene, vol. 60, no. 4, pp. 587–592, 1999.
[18] M. J. Blaser, "Role of vacA and the cagA locus of Helicobacter pylori in human disease," Alimentary Pharmacology and Therapeutics, Supplement, vol. 10, supplement 1, pp. 73–77, 1996.
[19] S. J. Spechler, L. Fischbach, and M. Feldman, "Clinical aspects of genetic variability in Helicobacter pylori," Journal of the American Medical Association, vol. 283, no. 10, pp. 1264–1266, 2000.
[20] Z. Xiang, S. Censini, P. F. Bayel et al., "Analysis of expression of CagA and VacA virulence factors in 43 strains of Helicobacter pylori reveals that clinical isolates can be divided into two major types and that CagA is not necessary for expression of the vacuolating cytotoxin," Infection and Immunity, vol. 63, no. 1, pp. 94–98, 1995.
[21] T. Wiedemann, E. Loell, S. Mueller et al., "Helicobacter pylori cag-pathogenicity island-dependent early immunological response triggers later precancerous gastric changes in Mongolian gerbils," PLoS ONE, vol. 4, no. 3, Article ID e4754, 2009.
[22] P. Olbermann, C. Josenhans, Y. Moodley et al., "A global overview of the genetic and functional diversity in the Helicobacter pylori cag pathogenicity island," PLoS Genetics, vol. 6, no. 8, Article ID e1001069, 2010.
[23] M. Hatakeyama, “SagA of CagA in Helicobacter pylori pathogenesis,” Current Opinion in Microbiology, vol. 11, no. 1, pp. 30–37, 2008.

[24] J. Wei, T. A. Nagy, A. Vilgelm et al., “Regulation of p53 tumor suppressor by Helicobacter pylori in gastric epithelial cells,” Gastroenterology, vol. 139, no. 4, pp. 1333–1343, 2010.

[25] J. P. Thiery, “Epithelial-mesenchymal transitions in tumor progression,” Nature Reviews Cancer, vol. 2, no. 6, pp. 442–454, 2002.

[26] J. Kountouras, C. Zavos, D. Chatzopoulos, and P. Katsinelos, “New aspects of Helicobacter pylori infection involvement in gastric oncogenesis,” Journal of Surgical Research, vol. 146, no. 1, pp. 149–158, 2008.

[27] J. Lan, Y. Xiong, Y. Lin et al., “Helicobacter pylori infection generated gastric cancer through p53-Rb tumor-suppressor system mutation and telomerase reactivation,” World Journal of Gastroenterology, vol. 9, no. 1, pp. 54–58, 2003.

[28] F. Shanahan, “Gut microbes: from bugs to drugs,” American Journal of Gastroenterology, vol. 105, no. 2, pp. 275–279, 2010.

[29] B. Terrier, D. Séne, D. Saadoun et al., “Serum-free light chain assessment in hepatitis C virus-related lymphoproliferative disorders,” Annals of the Rheumatic Diseases, vol. 68, no. 1, pp. 89–93, 2009.
