Helicobacter pylori infection. Several studies on pathology and clinicopathology

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Chapter 7

Summary
SUMMARY

Since the updated Sydney system was introduced in 1994, several studies on interobserver variation in the assessment of *H. pylori*-associated gastritis have been reported. Chapter 2 describes our study on interobserver variation of histological variables of *H. pylori*-associated gastritis in gastric antral mucosa by two independent pathologists, using the updated Sydney system for classification of chronic gastritis. Two hundred and ninety dyspeptic Dutch patients with biopsy proven *H. pylori* infection were enrolled in the study. Gastric antral mucosal biopsy specimens were analysed before and after *H. pylori* eradication treatment. Variables analysed included the density of *H. pylori* infection, the degree of chronic inflammation, inflammatory activity, atrophy, intestinal metaplasia (IM), and surface epithelial damage (SED). Before grading biopsy specimens, both pathologists reached a consensus on the scoring of gastritis through interactive sessions using a multiheaded microscope. Interobserver variability was also analysed using weighted $k$ scores. The overall interobserver agreement on the scoring of the various gastritis features was high. Agreement on grading of atrophy was the lowest; however, moderate to good reproducibility was achieved ($k=0.49-0.52$). Disagreement was most common in biopsy specimens with lesser degrees of atrophy. A high degree of agreement was obtained for IM ($k=0.72-0.73$). The best agreement was reached in the assessment of the density of *H pylori* both before
and after H. pylori eradication treatment ($k=0.76\sim0.95$). The grade of reproducibility of inflammatory activity, SED, and chronic inflammation was also high ($k=0.60\sim0.83$). We concluded that reproducibility of grading H. pylori related gastritis is high using the updated Sydney system. Despite the novel criteria for scoring atrophy, there was imperfect agreement on this feature between two independent pathologists.

It has now been established that infection with H. pylori should be regarded as a definitive cause of human gastric cancer and has been classified as a class I carcinogen exposure by the International Agency for Research on Cancer (IARC) in 1994. The most important epidemiological evidence supporting the association was that provided by several prospective studies which showed that infected individuals have a four-fold increased risk of subsequently developing gastric cancer. Atrophy and IM as precancerous conditions are serious consequences of H. pylori-associated infection. Geographical variation in the incidence and severity of these pathological lesions has been related to the difference in the incidence of gastric cancer. To understand the differences in the incidence of gastric cancer between various populations there is a need to study whether atrophy and IM also differ between the high and low incidence countries. Our study was designed to compare the discrepancies of atrophy and IM in the antral mucosa among Chinese and Dutch patients infected with H. pylori. Chapter 3 reports the discrepancies in the prevalence and the severity of precancerous conditions-atrophy and IM in antral mucosa of H.pylori-associated gastritis and difference in age of onset among
Chinese and Dutch patients. Two hundred and sixty five Chinese patients and 261 Dutch patients with *H. pylori* infection were enrolled. The degrees of atrophy and IM were graded according to the updated Sydney system. The overall prevalences of atrophy and IM were lower in Dutch patients (42% and 26%, respectively) than in Chinese patients (52% and 32%, respectively). Only the difference in atrophy reached significance (p=0.028). However, in both Chinese and Dutch patients, the degrees of atrophy and IM were low and severe degrees were rare. The mean ages of Chinese and Dutch patients with atrophy and IM were higher than those without atrophy and IM. Atrophy and IM occurred earlier and were more severe in Chinese patients, with both reaching a peak value in patients over 60 years. We concluded the there are geographical differences in the prevalence and severity of *H. pylori* infected gastritis, in particular with respect to atrophy and IM, among Chinese and Dutch patients.

In 1988, it was recognized that the mucosa-associated lymphoid tissue (MALT) is a consequence of *H. pylori*-associated gastritis. The results of the epidemiological study showed that MALT lymphoma occurs more frequently in the region of high incidence of *H. pylori* than in comparable regions with a low incidence. *H. pylori* was indeed a prelymphoma condition. To examine the relationship between *H. pylori* and the development of lymphoid tissue hyperplasia, we investigated the evolution between lymphoid follicles and aggregates and other histopathologic features during the 2-year observation period after eradication of *H. pylori*. Chapter 4 reports the relationship between lymphoid tissue hyperplasia and
H. pylori-associated gastroduodenal diseases in the antrum and its evolution after eradication of H. pylori. Gastric antral biopsy specimens were obtained from 438 patients with H. pylori-positive gastroduodenal diseases (185 chronic gastritis, 69 gastric ulcer and 184 duodenal ulcer) and 50 H. pylori-negative healthy controls. Lymphoid follicles and aggregates were counted and other pathologic features were scored according to the updated Sydney system for classification of chronic gastritis. After a course of anti-H. pylori therapy, biopsy specimens were obtained at 4-6 weeks, 12 and 24 months in the chronic gastritis patients group. Total prevalence of lymphoid follicles and aggregates in the biopsies was 79.9% (350/438). The prevalence and density of lymphoid follicles and aggregates were significantly different in the various gastroduodenal diseases. The highest prevalence and density of lymphoid follicles and aggregates occurred in patients with gastric ulcer (89.9% and 0.82, respectively). The lowest prevalence of lymphoid follicles and aggregates was found in 74.6% in patients with chronic gastritis, and the lowest density of lymphoid follicles and aggregates was detected in 0.56 in patients with duodenal ulcer. The prevalence and density of lymphoid follicles and aggregates correlated strongly with the activity and severity of gastric antral inflammation. Eradication of H. pylori resulted in a decrease in the prevalence and density of lymphoid follicles and aggregates. We concluded that prevalence and density of lymphoid follicles and aggregates in gastric antral mucosal biopsies correlated closely with H. pylori infection.

The severity of gastritis and the effect of therapeutic intervention are related to
differences in virulence of \textit{H.pylori} strains. The vacuolating cytotoxin produces massive vacuolation in several mammalian cell lines. It's believed to produce similar damage in gastric epithelial cell in \textit{vivo}. All strains contain the \textit{vacA} gene, although not all produce the toxin. Our study shows that the role of the vacuolating cytotoxin activity (VacA) appears to be less important in Chinese populations when contrasted with the western experience. Chapter 5 reports whether VacA has any influence on the gastric mucosal changes prior to and after \textit{H.pylori} eradication in Chinese patients with peptic ulcer disease and chronic gastritis. Seventy-four consecutive dyspeptic Chinese patients with \textit{H.pylori} infection were enrolled. The status of \textit{H.pylori} infection was evaluated by culture and histopathology before and 4-6 weeks after \textit{H.pylori} eradication therapy. Histologic specimens were examined and graded semiquantitatively according to the updated Sydney classification. VacA+ \textit{H.pylori} organisms were isolated from 59/74 (80%) patients, its prevalence in peptic ulcer disease / chronic gastritis and the results after eradication were similar in those with VacA+ and VacA- \textit{H.pylori} strains. The degree of acute or chronic inflammation, SED, atrophy, IM and the number of lymphoid follicles were similar in patients with VacA+ and VacA- \textit{H.pylori}. Six weeks after eradication of \textit{H.pylori} infection, the degree of acute and chronic inflammation, SED decreased significantly, particularly in those with VacA+ \textit{H.pylori} (p < 0.0001), whereas the number of lymphoid follicles in the antrum also diminished more in those with VacA+ \textit{H.pylori} (p=0.051). However, the degree of atrophy and IM varied somewhat, there had been no improvement in the former but moderate improvement in the latter
We concluded that there is no specific correlation between VacA positive or negative *H. pylori* strains and clinicopathological features among Chinese patients with peptic ulcer and chronic gastritis. Successful eradication of *H. pylori* infection dose not improve atrophic lesion of gastric mucosa, but there is some extent of improvement of IM. However the number of patients was small in the subgroup, and the follow-up period was relatively short, which requires long-term study with extensive follow-up.

The inducible cyclooxygenase (COX-2) is an important regulator of mucosal inflammation. Although it's unknown how infection with *H. pylori* induces expression of COX-2 in gastric mucosal cells. Recent studies indicate that COX-2 may play an important role in gastrointestinal inflammation and carcinogenesis. In this study, we design to investigate the effects of *H. pylori* infection on COX-2 expression in gastric antral mucosa before and after antibiotics therapy using immunohisto-chemistry.

Chapter 6 reports the correlation between COX-2 protein expression and inflammation in *H. pylori* infected antral mucosa and its evolution after anti-*H. pylori* treatment. Antral biopsies were taken from 46 patients with *H. pylori*-related chronic gastritis both before and after eradication of *H. pylori*. COX-2 protein was stained by immunohistochemistry and expressed as a percentage of the total number of epithelial cells. Cytoplasmic staining of COX-2 protein could be detected in epithelial cell both before and after eradication of *H. pylori*. The expression of COX-2 protein was significantly higher in *H. pylori*-infected mucosa. Successful eradication of *H. pylori* resulted in a decrease in COX-2 expression. COX-2
immunostaining was correlated with the degree of chronic inflammation. We concluded that *H. pylori* infection leads to gastric mucosal overexpression of COX-2 protein, suggesting that the enzyme may contribute to *H. pylori*-related gastric pathology in humans.

The contribution of the thesis to the understanding of pathologic features of *H. pylori*-associated gastritis with emphasis on precancerous conditions - atrophy and IM, and prelymphoma condition - lymphoid tissue hyperplasia, and reproducibility of grading gastritis features using the updated Sydney system, and the role of virulence factor-VacA in Chinese populations, and effects of *H. pylori* infection on COX-2 express in gastric mucosa, which can be encapsulated as follows:

Infection with *H. pylori* has been classified as a class I carcinogenic exposure by IARC. Atrophy and IM as precancerous conditions are serious consequences of *H. pylori*-associated infection. Geographical variation in the incidence and severity of these pathological lesions has been related to the difference in the incidence of gastric cancer. Our study shows that the differences in the incidence of gastric cancer between various populations (Chinese and Dutch) which atrophy and IM also differ between the high and low incidence countries. Atrophy and IM occurred earlier and were more severe in Chinese patients. It's now clear that lymphoid follicles and aggregates are characteristic of *H. pylori*-associated gastritis. The results of the epidemiological study showed that MALT lymphoma occurs more frequently in the region of high incidence of *H. pylori* than in comparable regions.
with a low incidence. The present study shows a very high frequency of lymphoid follicles and aggregates in Chinese patients with several *H. pylori* related gastric conditions, especially in gastric ulcer patients. This finding indicates that lymphoid tissue reaction is stronger in this population than in western population, which is parallel to infection with *H. pylori* occurs earlier in life and has a higher prevalence in China. This study is based on large number of patients and the results are largely confirmatory. The severity of gastritis and the effect of therapeutic intervention are related to differences in virulence of *H. pylori* strains. Our study shows that VacA positive *H. pylori* strains do not cause more significant alterations or diseases than VacA negative strains among Chinese patients, which suggests differences in host response to the infection are even more mysterious. COX-2 is an important regulator of mucosal inflammation. It's still unknown how infection with *H. pylori* induces expression of COX-2 in gastric mucosal cells. Our study shows that *H. pylori* leads to COX-2 protein overexpression in gastric antral mucosa, suggesting it may play an important role in gastric inflammation and carcinogenesis. Finally, the updated Sydney system for scoring *H. pylori*-associated gastritis is useful and reproducible, but there need to be improvement in the criteria for grading atrophy. Although several issues of *H. pylori* infection with emphasis on pathology and clinico-pathology have been studied extensively in the thesis, there are still many questions remained which need to be answered in the near future in this field.