Helicobacter Pylori and Gastric Precancerous Lesions: An update

Helikobakter Piliro ve Meniden Prekanseröz Lezyonları: Bir Güncelleme

Ibrahim Koral Onal¹, Mevlut Kurt², Nasser Alizadeh¹, Fatih Saygili³, Mehmet Ibis¹, Ramazan Yildiz⁴

¹ Department of Gastroenterology, Gazi University Medical School, Ankara, Turkey
² Department of Gastroenterology, Abant Izzet Baysal University Medical School, Bolu, Turkey
³ Department of Gastroenterology, Turkey İhtisas Education and Research Hospital, Ankara, Turkey
⁴ Department of Medical Oncology, Gazi University Medical School, Ankara, Turkey

ABSTRACT

Gastric cancer (GC) develops through a multistep process known as the gastritis-atrophy-metaplasia-dysplasia-cancer sequence associated with alterations in the expression of host oncogenes and tumor suppressor genes after several decades. Helicobacter pylori (H. pylori) infection is the most consistent risk factor for GC, and its elimination is, therefore, the most promising strategy to reduce the incidence of this malignant disorder. However, the results of the relevant studies are controversial as to whether the H. Pylori eradication effectively induces the regression of gastric preneoplastic lesions. The inconsistencies are likely due to the heterogeneity in studies with respect to the number of biopsy samples taken, the method of histologic classification of findings, sample size, and the duration of the follow-up. Additionally some probable or well-defined factors other than H. Pylori may influence the progression of gastric preneoplastic lesions. Lastly, the real existence of a "point of no return" may partially explain the controversial findings. Here, we present an index case, and review data about the role of H. pylori during gastric carcinogenesis, and subsequently discuss information available from recent studies to evaluate the benefit of the H. pylori eradication for the regression of gastric precancerous lesions.

Key Words: Atrophic gastritis, gastric cancer, Helicobacter Pylori, metaplasia, prevention, precancerous conditions

INTRODUCTION

Association between H. pylori and gastritis was recognized since 1970s, but in 1982 H.pylori was cultured as a gastric bacterium, and now, it is a known cause of gastritis, many of gastric and duodenal ulcers, gastric cancer (GC) and mucosa associated lymphoid disease (1-11). Worldwide, gastric cancer is one of the most common cancers, and H. pylori infection seems to be a necessary, although not sufficient, cause of GC (12-16). Many studies have provided data that the eradication of H. pylori could reduce the occurrence of peptic ulcer and GC (1,3-11). But there is still controversy about whether eradication of H. pylori enhances the regression of gastric precancerous lesions and virtually eliminates the risk of GC. Here, we present an index case, and review the data about the role of H. pylori during gastric carcinogenesis, and subsequently discuss the information available from recent studies to evaluate the benefit of the H. pylori eradication for the regression of gastric precancerous lesions.

ÖZET


Anahtar Sözcükler: Atrofik gastrit, gastrik kanser, Helikobakter piliro, metaplazi, önleme, prekanseröz durumlar

CASE REPORT

A 49-year-old, male patient was admitted to our clinic with the complaint of epigastric pain. He reported a previous history of H. Pylori infection but he could not remember whether he had an eradication therapy. Upper gastrointestinal endoscopy (UGE) was performed to see a flat lesion measuring 1.5 cm in diameter in the gastric antrum. Endoscopic biopsy sample of the lesion was consistent with a low-grade dysplasia whereas there were H. Pylori gastritis and intestinal metaplasia in the gastric corpus and neighbouring antrum. The flat lesion was removed by an endoscopic mucosal resection, and a low grade dysplasia with negative resection margins was detected on a pathological examination. Bismuth containing quadruple therapy was administered to treat H. Pylori, and an urea breath test one month after the therapy confirmed the clearance of microorganisms. A follow-up UGE after 6 months revealed a new flat lesion measuring 1.5 cm diameter in the corpus.

Address for Correspondence / Yazışma Adresi: Ibrahim Koral Onal, MD, Department of Gastroenterology, Gazi University Medical School, Besevler, 06560, Ankara, Turkey, E-mail: koronal@yahoo.com
©Copyright 2015 by Gazi University Medical Faculty - Available on-line at web site http://medicaljournal.gazi.edu.tr/ doi:http://dx.doi.org/10.12996/gmj.2015.38
The biopsy was consistent with adenocarcinoma, and the patient underwent a total gastrectomy and lymph node dissection. Pathological examination revealed an early gastric cancer and negative lymph nodes. The patient is still free of recurrence one year after the surgical therapy.

Our case was a good example of H. pylori associated gastric preneoplastic and neoplastic conditions showing that H. pylori gastritis, intestinal metaplasia, dysplasia and early gastric cancer could be diagnosed in the same patient. And the reason why the H. pylori eradication was not successful to prevent the development of gastric cancer in this patient is addressed in the following sections.

H. pylori and Gastric Carcinogenesis

GC is categorized as intestinal- or diffuse-type according to the presence or absence of glandular pattern. It has been hypothesized that GC develops through a multistep process known as the gastritis-atrophy-metaplasia-dysplasia-cancer sequence that is associated with alterations in the expression of host oncogenes and tumor suppressor genes after several decades (17-19). H. pylori is the most common factor in the development of GC via this sequence, but its role is not completely known (20). H. pylori is a gram-negative, spiral-shaped pathogen that colonizes the stomach of about half of the world’s population (17,18). The bacterium type IV secretion system. In the host cells, CagA localizes to the inner leaflet of the plasma membrane, where it undergoes tyrosine phosphorylation by Src or c-Abl kinase to disrupt tight junctions and epithelial apical-basolateral polarity (35-40). CagA binds to and inhibits partition-defective-1b (PAR1b)/microtubule affinity-regulating kinase-2 (MARK2) polarity-regulating kinase to disrupt tight junctions and epithelial apical-basolateral polarity (35-37). The antral mucosa is protected by Gastrin 1 (GKN1), which supports the host immune response, and inhibits CagA/SHP-2 complex formation. It was already mentioned that H. pylori infection is the most consistent risk factor for gastric cancer and its elimination is, therefore, the most promising strategy to reduce the incidence of gastric cancer (8). Based on the strong association between H. pylori and gastric cancer and Correa hypothesis (46), one would expect this bacterium to accelerate the development and/or progression of gastric preneoplastic lesions and antibacterial eradication treatment would be considered as a unique opportunity as a chemo-preventive strategy against the gastric cancer. However the results of the relevant studies are controversial as to whether H. pylori eradication effectively induces the regression of gastric preneoplastic lesions (47-49). A variety of reasons may explain this contradiction: First, the studies are heterogenous with respect to the number of biopsy samples taken, the method of histologic classification of findings, sample size, and the duration of the follow-up. Second, there are some probable or well defined factors other than H. pylori, which may influence the progression of gastric preneoplastic lesions. As a result, this observation is a clue that CagA-deregulated b-catenin is involved in the progression of intestinal metaplasia, a precursor of, gastric cancer (57,58). And lastly, the real existence of a “point of no return” may partially explain the controversial findings. The term ‘point of no return’ has been defined as the point in a sequence of events when it is no longer possible to reverse the course or stop the process. Actually it should be considered that gastric lesions like intestinal metaplasia or dysplasia, may be a biomarker associated with an increased risk for, rather than the precursor of, gastric cancer (57,58).

H. pylori Eradication and Atrophic Gastritis

The data of various published studies were pooled in two meta-analyses in an effort to answer the critical question of whether atrophic gastritis (AG) of the stomach is reversible after the H. pylori eradication (49,50). In the first meta-analysis (2007), the pooled odds ratio with 95% confidence interval (CI) was 0.554 (0.372-0.825) with a test for overall effect Z = -2.91 and p = 0.004 for antrum AG whereas it was 0.209 (0.081-0.538), Z = -3.24, p < 0.001 for corpus AG (57). These results indicated that H. pylori eradication has beneficial long-term effects on AG (59). In the second meta-analysis (2011), the inverse variance weighted mean differences (WMD) and 95% CIs for gastric atrophy and intestinal metaplasia-dysplasia-cancer sequence (17-19). H. pylori gastritis, intestinal metaplasia, dysplasia and early gastric cancer could be diagnosed in the same patient. And the reason why the H. pylori eradication was not successful to prevent the development of gastric cancer in this patient is addressed in the following sections.
In a recent randomised, placebo controlled trial designed to evaluate the effect of a selective cyclooxygenase-2 inhibitor alone and combined with H. pylori eradication on the evolution of precancerous gastric lesions, more than half of the participants (56.5%) with severe AG at baseline persisted in this state or reverted to a lesser lesion (60). A randomized double-blind study in the first-degree relatives of gastric cancer patients showed that a regression was observed in 61.8% of the patients for antral AG and in 35.6% of the patients for corporal AG following the H. pylori eradication (P<0.0001 as compared with non-eradicated group) (61). All these results are generally in good agreement with those obtained from Correa’s studies, which showed that an effective anti-H. pylori treatment may interfere with the precancerous process, by increasing the rate of regression of AG (62). This regression of atrophy was further confirmed after a 12-year-follow-up (63).

As a conclusion, a multidisciplinary panel agreed that the H. pylori eradication may lead to a partial regression of AG although it is unclear whether the effects of the treatment vary with the location and the extent of atrophy (64).

H. pylori Eradication and Intestinal Metaplasia

Correa et al. showed that anti-H. pylori treatment resulted in a reduced risk of progression in gastric preneoplastic lesions (17% vs 23% in placebo group) at the end of a 6-year-follow up (62). Later extension of this study showed a significant reduction in the histopathology score as a function of the square of the H. pylori negative time (63). Additionally, 20% (70/182) of subjects with IM at baseline who were H. pylori negative at 12 years had no atrophy or IM at that point, as compared with 5% (9/183) among those who were H. pylori positive (63). But these results were not confirmed by two meta-analyses, which revealed that no improvement was shown for IM following the H. pylori eradication (49,59). A recent study did not find statistically significant beneficial effects on the progression of advanced gastric lesions after the H. pylori eradication, and only about one third of participants with IM at baseline persisted in this state or reverted to a lesser lesion (60). Massarrat et al. reported that the regression of IM occurred in the antrum of corpus of the treated subjects over four-and-a-half years but progression of IM in the antrum was more frequent in non-H. pylori eradicated patients (18.8% vs 5.9% p < 0.05) (61). This finding was consistent with the results of another study which showed that the persistent H. pylori infection was an independent risk factor associated with the IM progression (OR 2.13 (95% CI 1.41–3.24)) (65). As a conclusion, it has been generally agreed that the H. pylori eradication does not appear to reverse IM but it may slow its progression to neoplasia, and therefore, is recommended (65).

H. pylori Eradication and Dysplasia

Although the end of the Correa process, gastric cancer, is reached in only about 5% of patients with advanced AG/IM, Correa’s sequence is still widely preferred to define the progression or the regression of gastric precancerous lesions (66). Accordingly, the regression of dysplasia following the H. pylori eradication would not be expected because such an effect could not be observed in the time course of IM (60,61,64). In fact, relevant studies confirmed this expectation that dysplastic lesions are not affected by eradication. At the end of a 12-year-follow up period following the H. pylori eradication, Mera et al. found no significant changes in dysplasia (63). Among the nine new gastric cancer cases during this period, five were in the H. pylori treatment group with four dysplasia and one IM at baseline (63). In another long-term-follow up study, H. pylori treatment did not significantly reduce the combined prevalence of dysplasia or gastric cancer (47). Among subjects who had dysplasia in 1994, six (4.2%) progressed to gastric cancer with the active H. pylori treatment, and 10 (6.6%) progressed to gastric cancer with placebo in 2003 in this study (47). A recent study showed that the H. pylori eradication or celecoxib treatment may enhance the regression of advanced gastric lesions but no statistically significant effects were observed in any histopathology categories including dysplasia by treatment arm (60). Longer follow up studies with adequate sample sizes may answer the question of the effect of H. pylori clearance on dysplasia.

H. pylori Eradication for the Prevention of Metachronous Neoplastic Lesions

It is still not clear whether the H. pylori eradication can reduce the incidence of metachronous cancer after endoscopic resection in patients with gastric dysplasia or cancer. In a multi-centre, open-label, randomised controlled trial, 546 patients with an early gastric cancer, were randomly assigned to receive an H. pylori eradication regimen (n=272) or to be in the control group (n=272) (67). At the 3-year follow-up, a metachronous gastric carcinoma was detected in 9 patients in the eradication group and 24 in the control group. In the modified intention-to-treat population, adjusting for the loss to follow-up, the hazard ratio for metachronous gastric cancer was 0.339 (95% CI 0.157-0.729; p = 0.003) (67). The authors concluded that the H. pylori eradication after endoscopic resection of early gastric cancer could prevent the development of metachronous gastric carcinoma (67). But a recent prospective, randomised controlled trial did not confirm the findings from this dataset. In this study, 10 out of 444 patients in the eradication group and 17 out of 457 patients in the control group developed metachronous gastric carcinoma during a median follow-up period of 3 years, and the difference was not significant (p=0.15) (68). In a retrospective study, it was shown that metachronous gastric cancer developed in 13 patients (14.3%) in the H. pylori persistent group, and in 15 patients (8.5%) in the eradicated group (p = 0.262) during an overall follow-up period ranging from 1.1 to 11.1 years (median 3.0 years) (69). A multivariate logistic regression analysis indicated that the baseline severe mucosal atrophy and a follow-up of more than 5 years were independent risk factors for the development of metachronous gastric cancer (69). As a conclusion, further research into the role of H pylori eradication after endoscopic resection in patients with gastric tumors is warranted.

CONCLUSION

H. pylori-associated chronic active inflammation may initiate numerous genetic and epigenetic events which may result in gastric cancer, and CagA gene is critical for the activation of oncogenetic pathways. The H. pylori eradication may lead to a partial regression of AG, but it does not seem to reverse IM or dysplasia. However, the H. pylori eradication may slow the progression of gastric preneoplastic lesions to neoplasia, and therefore, is recommended.

Conflict of Interest

No conflict of interest was declared by the authors.

REFERENCES

GMJ 2015; 26: 121-124
Helicobacter Pylori and gastric lesions

Onal et al.


