THE OCCURRENCE OF SIEVE-LIKE DUODENUM DUE TO *HELICOBACTER PYLORI* INFECTION IN A CIRRHOTIC PATIENT: CURRENT INSIGHTS, MANAGEMENT, AND THE IMPORTANCE OF *H. PYLORI* INFECTION AND ITS ASSOCIATIONS WITH CIRRHOSIS

Cyriac Philips[*,1] **and Chhagan Bihari**[**]

[*]Department of Hepatology and Transplant Medicine Institute of Liver and Biliary Sciences D-1, Vasant Kunj, New Delhi, India., [**]Department of Pathology Institute of Liver and Biliary Sciences D-1, Vasant Kunj, New Delhi, India.

ABSTRACT

Helicobacter pylori infection is prevalent worldwide. Involvement of H. pylori in the aetiopathogenesis of liver diseases are a matter of debate. Treatment options vary widely among different regions with regards to microbial sensitivity patterns. In this short review, we present the case of an alcoholic cirrhosis patient, who presented with a rare 'sieve-like' appearance of the duodenum secondary to multiple ulcers, due to H. pylori infection.. We review briefly, but concisely, the different associations and strengths of H pylori with liver disease and recent guidelines and recommendations on treatment of this widely present infection.

KEYWORDS Cirrhosis, Portal hypertension, Helicobacter pylori, NAFLD, HCV, HCC, Duodenal ulcer, Gastritis

Introduction

Helicobacter pylori is a gram-negative, micro-aerophilic spiral shaped flagellated bacterium, which colonizes the human gastric mucosa leading to a persistent infection with or without clinical consequences. It affects around 75% of human population over the world and is thought to be among the most common bacterial infections in humans. There are several clinical afflictions associated with H. pylori, such as gastric and duodenal ulcers, chronic gastritis, gastric malignancy, and gastric and small intestinal mucosa-associated lymphoid malignancy. Chronic H. pylori infection has been implicated in metabolic disorders with persistent low-grade systemic inflammation and non-gastrointestinal diseases such as chronic urticaria. The chronic H. pylori infection has also been incriminated in development and complications related to chronic liver diseases such as non-alcoholic fatty liver disease and hepatic encephalopathy [1]. In this short communication, we discuss a patient with compensated alcoholic cirrhosis, abstinent since one year, with chronic nonspecific dyspeptic symptoms, in whom, upper gastrointestinal endoscopy revealed multiple scarred and healed ulcerations of the first and second part of duodenum leading to a 'sieve-like' appearance. We discuss current guidelines for treatment of H. pylori and importance of this joint infection in cirrhotics [1].

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[1]Cyriac Abby Philips, Department of Hepatology and Transplant Medicine, Institute of Liver and Biliary Sciences D-1, Vasant Kunj, New Delhi, India
Email: abbyphilips@gmail.com

Case report

A 46-year-old man diagnosed with alcoholic cirrhosis without any known comorbidity but having dyspepsia, bloating, early satiety and abdominal discomfort lasting for six months was referred to us by his local physician for the evaluation of thrombocytopenia and bilateral symmetrical feet swelling. The patient did not experience any episode of gastrointestinal bleed-

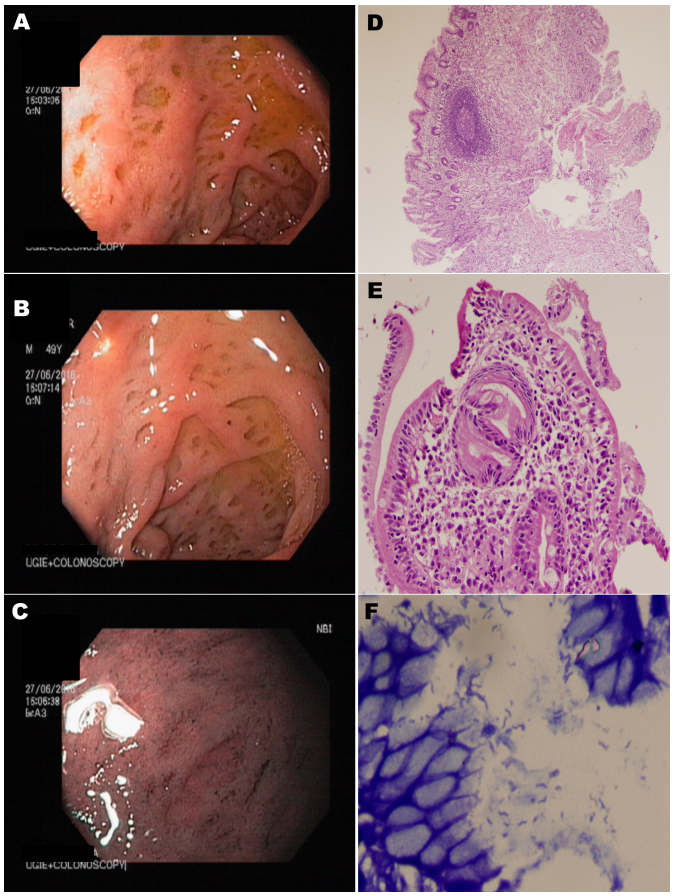

Fig.1 Upper gastrointestinal endoscopy showing multiple excavated mucosal lesions in first part of duodenum (A) and similar lesions in second part of duodenum (B) with a "sieve like" mucosal appearance.

ing, abdominal distension, altered bowel habit, sleep reversal, jaundice, long-standing recurrent fever, and weight loss. He also reported on not using any over the counter analgesic or complementary and alternative medicine. According to our physical examination, he can be described as an overweight (body mass index 29.1), co-operative, and oriented patient without peripheral signs of liver cell failure or ascites. The firm left lobe of the liver was palpable with splenomegaly and at least four spider angiomas over the upper chest and limbs. His blood investigation was positive for low platelet counts, hypoalbuminemia, and mildly raised the uric acid level. Upper gastrointestinal endoscopy revealed small low-risk esophageal varices without portal hypertensive gastropathy or gastric vascular ectasia. However, mucosa of the first and second part of the duodenum showed multiple extensive healed ulcers with scarring, loss of normal mucosal fold and pattern giving rise to a "sieve-like" mucosal appearance (Figure 1, A-C). The biopsy of the gastric and duodenal mucosa revealed features of chronic gastritis (Figure 1D) and duodenitis (Figure 1E), with an association of H. pylori (Figure 1E) suggesting an active infection. The patient was given omeprazole, amoxicillin, and tinidazole based antimicrobial therapy for two weeks followed by 20 mg of omeprazole daily for four weeks. At one-month followup, the patient's gastrointestinal symptoms reduced to 80% with improvement in overall quality of life.

Discussion

A. Helicobacter pylori infection and liver disease

Cirrhotics have a higher frequency of developing peptic ulcers (approximately 20%) than the general population (4%). Various studies have shown an association between Helicobacter species and the diseases of the hepatobiliary system in animals with chronic hepatitis, hepatobiliary fibrosis, and hepatobiliary malignancies. Similarly, many studies have detected various Helicobacter species, by employing polymerase chain reaction for 16s rDNA and specific gene, in the liver of patients having hepatocellular carcinoma. The hepatic encephalopathy—a complex neuropsychiatric complication in cirrhosis—has been postulated to be associated with the pathogenic mechanisms of H. pylori infection (i.e., ammonia splitting activity of urease enzyme). Therefore, the eradication of H. pylori decreased the frequency of encephalopathy episodes. Even though relations have been shown, it is still not clear which species of Helicobacter is associated with the onset of liver disease in humans. In one particular case, H. pylori were cultured and isolated from the stool sample of a patient of Wilson's disease. Further studies attempting to delineate any relation between causes and assumptions of Helicobacter species and liver disease ended up with ambiguous results [2, 3]. A large meta-analysis done in 2014 by Feng and colleagues found that the prevalence of H. pylori infection (detected by ELISA) in cirrhotic patients had increased significantly worldwide in the patients with viral and primary biliary cholangitis related to the chronic liver disease. However, this meta-analysis had some limitations as many published studies in various databases were left out and only 'healthy' patients were included [4, 5]. Similar to this meta-analysis, other studies have also shown a strong association of H. pylori with viral hepatitis related cirrhosis, especially hepatitis C (HCV) infection. Wang and co-workers conducted a trial sequence analysis along with the meta-analysis of studies on HCV and H. Pylori and demonstrated a positive association between the two and revealed strong correlations of H. pylori infection with HCV cirrhosis and HCV-related hepatocarcinogenesis. They also recommended H. pylori screening in the HCV-related chronic liver disease population. However, this meta-analysis included only case-control studies and not well designed randomized control trials. Moreover, few studies were inarguably left out from the meta-analysis, and the H. pylori detection methodology varied considerably within the included studies. Hence, there is no convincing report establishing a strong association of H. pylori with HCV and HCC [6]. The role of H. pylori in causation and progression of metabolic diseases has been well described; and in light of it, the evidence for causality associated with non-alcoholic fatty liver disease (NAFLD) and gut microbiota dysbiosis with the importance to Helicobacter species can be gleaned [7, 8].

The effect of Helicobacter pylori eradication, which evaluated the effect of H. pylori eradication on liver fat content, liver function test (LFT) and metabolic parameters in NAFLD patients, was determined by the researchers from Tehran in a randomized open-label clinical trial. They showed that H. pylori eradication has no additional effect on the changes in the metabolic indices. Previous studies showed a positive correlation of H. pylori with metabolic syndrome and an inverse correlation with morbid obesity and proposed that increased ghrelin following by H. pylori treatment improve the appetite and led to weight gain. It was also noted that H. pylori eradication in dyspeptic NAFLD patients did not provide any additional improvement

in liver fat content, LFT, fasting serum glucose, lipid profile, insulin resistance, and anthropometric measurements compared to lifestyle modification alone [9].

Okushin and co-workers, in 2015, performed a cross-sectional study on 13,737 subjects in Japan and reported no association of H. pylori with NAFLD. Similarly, in 2016, Baeg and colleagues, using a retrospective cohort of 3663 patients, investigated the association between H. pylori infection and NAFLD by using two non-invasive scoring parameters: NAFLD-fat score and hepatic steatosis index; and they showed that H. pylori infection is not a risk factor for NAFLD by either parameter [10, 11]. Many initial studies on H. pylori and cirrhosis shed light on the association of infection with portal hypertensive gastropathy (PHG). However, further studies failed to show similar findings on a large scale. Currently, the data on H. pylori and PHG are controversial, and the existing studies are inconclusive regarding the correlation between H. pylori and etiology, stage of cirrhosis, and presence and severity of PHG. Hence, the eradication strategies, once recommended in patients of severe PHG with H. pylori serology positive, are currently not warranted [12].

Quite recently, Zhang and colleagues conducted a multicenter observational study to assess the influence of H. pylori infection on the severity of thrombocytopenia and its treatment response in chronic hepatitis B (HBV) patients with compensated cirrhosis. Even though they did not find a strong correlation between H. pylori and HBV infection, the authors revealed that treating the patients having co-infection and eradicating H. pylori improved platelet counts in the patients who were on nucleoside analogs in comparison to those who were not [13].

In summary, the association between H. pylori and liver disease has some strength when it comes to viral hepatitis, but the correlations with NAFLD, hepatocarcinogenesis, and other portal hypertensive complications, such as PHG, are currently not strong enough.

B. Current guidelines in management of Helicobacter pylori infection and ulcer disease

i. General Recommendations: Patients with dyspeptic symptoms should be distinguished between those with organic (25%) and those with functional causes (75%). A pristine history and clinical examination are mandatory to assess red flag (alarming) symptoms (overt gastrointestinal bleeding, unexplained weight loss, progressive dysphagia, odynophagia, recurrent vomiting, and family history of gastrointestinal malignancy) and signs (anemia, abdominal mass, lymphadenopathy, organomegaly, and nutritional deficiencies). The patients with alarming features and/or above $\geq$ 55 years of age should be evaluated with early upper endoscopy and/or abdominal ultrasound. In the patients < 55 years of age with dyspeptic symptoms induced by NSAIDs, the treatment should be discontinued and proton pump inhibitors (PPI) for eight weeks should be tried. For the patients, manifesting with early satiety, gastric fullness, and vomiting, an empiric trial of prokinetic agents is recommended. In the case of persistent symptoms, further evaluation with endoscopy, imaging or scintigraphy, and breath tests need to be undertaken. Patients < 55 years of age without red flag features should be tested and treated for H. pylori [14].

ii. Tests and Evaluations for H. pylori: Non-invasive tests include, serology (blood IgG, salivary assay, and urinary IgG assay), urea breath tests (13C and 14C urea breath tests), urea blood test (13C urea blood test), stool antigen tests (polyclonal, monoclonal and rapid antigen; for confirmation of cure testing to be done six weeks after the end of therapy); invasive tests [endoscopy and biopsy sampling (four biopsy sites – lesser and greater curvature of the mid antrum and mid body) for rapid urease testing the use of large forceps/or multiple samples increases the sensitivity of the test as positive rapid urease test is based on the bacterial load in the gastric biopsy, immunostaining, fluorescent in situ hybridization, brush cytology], molecular testing for susceptibility, virulent factors (VacA or CagA), bacterial culture and susceptibility tests (after treatment failures only) [14].

iii. Guidelines for evaluation and management of H. pylori infection and peptic ulcer disease: A meta-analysis on the comparative effectiveness and the tolerance of treatments for H. pylori showed that concomitant treatments for 10 or 14 days of probiotic-supplemented triple treatment, 10 or 14 days of Levofloxacin-based triple treatment, 14 days of hybrid treatment, and 10 or 14 days of sequential treatment might be better alternatives for the eradication of H. pylori [15]. A Cochrane review concluded that a one to two weeks long course of H. pylori eradication therapy is an effective treatment for the people with H. pylori-positive duodenal ulcer when compared to no treatment or only ulcer healing therapy. It was explicitly stated that currently there is no evidence that H. pylori eradication therapy is an effective treatment in the people with gastric ulcer or that it is effective in preventing recurrence of duodenal ulcer compared to ulcer healing treatments [16].

a. The 2015 Japanese Society of Gastroenterology Clinical Practice Guidelines on the management of patients with peptic ulcer disease recommend that in cases with no NSAID use and H. pylori-positivity, the eradication therapy and anti-ulcer therapy should be concomitantly given. The eradication therapy includes triple therapy using PPI, amoxicillin, and clarithromycin, where the high-dose of PPI increases the efficacy of the therapy. There is no significant difference in cure rates among various PPIs (e.g., omeprazole, lansoprazole, rabeprazole, and esomeprazole). The sequential therapy and concomitant quadruple (PPI, clarithromycin, metronidazole, and amoxicillin; non-bismuth-containing) are also equally effective. If this fails, as the second-line of therapy, triple therapy with moxifloxacin is suggested or triple therapy with PPI, amoxicillin, and metronidazole) can be given (there is no third line therapy). In cases of H. pylori positive patients with no indication for eradication therapy, non-eradication therapy is provided. In the non-eradication therapy, the first choice is PPI therapy, and the second choice is histamine 2-receptor antagonist therapy followed by maintenance therapy for prevention of ulcer relapse [17].

b. Guidelines for the management of Helicobacter pylori infection in Italy: The III Working Group Consensus Report of 2015 recommended, first-line therapy with clarithromycin-containing triple therapy for 14 days (PPI, twice a day; clarithromycin, 500 mg twice a day; amoxicillin, 1000 mg twice a day; or metronidazole or tinidazole, 500 mg twice a day), or a sequential therapy for 10 days (PPI, standard dose twice a day) with amoxicillin (1000 mg twice a day) for first five days, followed by clarithromycin (500 mg twice a day) and metronidazole or tinidazole (500 mg twice a day) for next five days. In addition to this, they also recommend a concomitant therapy (non-bismuth quadruple) for ten days, which includes PPI, clarithromycin (500 mg twice a day), amoxicillin (1000 mg twice a day), metronidazole or tinidazole (500 mg twice a day). The recommended second-line of therapy is levofloxacin-containing triple therapy for ten days (PPI, twice a day with levofloxacin, 500 mg once a day or 250 mg twice a

day, amoxicillin, 1000 mg twice a day), or bismuth-containing quadruple therapy for 7–14 days (PPI, twice a daily; bismuth salts, four times a day; tetracycline, 500 mg three times a day; and metronidazole, 500 mg three times a day). In the event of the failure of second-line treatment with 10-days levofloxacin triple therapy, bismuth-containing quadruple therapy should be used as the third-line treatment, whenever bismuth salts are available or rifabutin-based regimen for refractory infection in whom all previous treatments have failed (dose of 300 mg daily, either 150 mg twice a day or 300 mg once day for 10 days), along with antibiotic susceptibility testing [18].

c. Kyoto global consensus report on Helicobacter pylori gastritis, 2015: According to this report, patients with dyspepsia, after negative routine laboratory and upper endoscopy except for positive H. pylori tests must undergo eradication therapy. In the event of symptomatic relief, the dyspeptic symptoms are considered as H. pylori-associated, but if the symptoms do not resolve or recur after eradication therapy, the possibility of functional dyspepsia is considered. The report observed that H. pylori eradication regimen depends on the pattern of resistance in the population and the common host genotypes of the drug metabolizing enzymes in the population; therefore, the preferred eradication regimen often differs between regions. Thus, within a region, only regimens that have reliably produced eradication rates of $\geq$ 90% in the same population should be used for empirical treatment [19].

d. The Toronto Consensus for the Treatment of Helicobacter pylori Infection in Adults, 2016: The group strongly recommended that all H. pylori eradication regimens should be given for 14 days. The recommended first-line strategies include concomitant non-bismuth quadruple therapy (PPI + amoxicillin + metronidazole + clarithromycin or PAMC), and traditional bismuth quadruple therapy (PPI + bismuth + metronidazole + tetracycline or PBMT). The PPI triple therapy (PPI + clarithromycin and either amoxicillin or metronidazole) should be avoided in the areas known to have low clarithromycin resistance. Recommended rescue therapies include PBMT and levofloxacin-containing therapy (PPI + amoxicillin + levofloxacin or PAL) with rifabutin-containing regimens restricted to the patients in whom at least three first options have already failed [20].

Conclusion

Even though H. pylori infection prevails worldwide, the treatment regimens vary from region to region. The association of H. pylori infection, progression, and complications of cirrhosis are still a matter of debate. Current guidelines recommend region specific treatment options, and such guidelines are of utmost importance in high prevalence areas with sensible antimicrobial therapy based approaches.

Disclosure Statement

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