Active peptic ulcer disease in patients with hepatitis C virus-related cirrhosis: The role of Helicobacter pylori infection and portal hypertensive gastropathy

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BACKGROUND & AIM: The relationship between Helicobacter pylori infection and peptic ulcer disease in cirrhosis remains controversial. The purpose of the present study was to investigate the role of H pylori infection and portal hypertension gastropathy in the prevalence of active peptic ulcer among dyspeptic patients with compensated hepatitis C virus (HCV)-related cirrhosis.

METHODS: Patients undergoing upper endoscopy with compensated HCV-related cirrhosis were enrolled. Child-Pugh's score was determined at the entry. Variceal size was measured endoscopically and the severity of portal hypertensive gastropathy was graded. H pylori infection status was determined by urea breath testing and/or histology.

RESULTS: A total of 178 patients positive for HCV (A and B Child-Pugh's score) were prospectively included. The prevalence of H pylori infection was 43%. An active peptic ulcer was found in 14 patients (8%) and was significantly more common among those with H pylori infection (16% versus 2% in H pylori uninfected patients, odds ratio: 8.0). No association was observed between H pylori infection and variceal size, or hypertensive gastropathy.

CONCLUSIONS: Patients with compensated cirrhosis and H pylori infection showed higher risk of developing a peptic ulcer. Clinical relevance of this result would be that dyspeptic patients with HCV-related cirrhosis may benefit from preventive screening and eradication of H pylori, especially those with features of insufficient hemostasis.

Key Words: Cirrhosis; Congestive gastropathy; Helicobacter pylori infection; Portal hypertension

The prevalence of peptic ulcer in patients with liver cirrhosis is increased compared with that in the general population, suggesting that factors such as congestive gastropathy associated with portal hypertension, impaired mucus and bicarbonate secretion and reduced mucosal prostaglandin levels may increase the risk to develop a gastric lesion (1,2). Although Helicobacter pylori is the major cause of peptic ulcers, the pathogenesis of ulcer disease in cirrhosis is unclear. Several studies have reported a relationship between H pylori and peptic ulcer in this population (3-5). Calvet et al (6) observed that male sex and H pylori seropositivity are significantly related to peptic ulcer disease in cirrhotic patients. Multivariate analysis showed that these factors were independently related to lifetime prevalence of peptic ulcer: male sex (OR 1.56, 95% CI 1.03 to 2.36), and seropositivity for H pylori (OR 1.65, 95% CI 1.15 to 2.37) (6). In a meta-analysis of 679 cirrhotic patients, Gisbert et al (7) reported higher prevalence of H pylori in patients with peptic ulcer disease...
and lung disease, or prior treatment for including acetylsalicylic acid, malignancy, severe heart, kidney, intestinal surgery, regular use of nonsteroidal anti-inflammatory drugs endoscopy were excluded. Other exclusion criteria included gastrointestinal compounds, antisecretory drugs or antibiotics four weeks before upper and medical history were recorded. Patients who received bismuth obtained by needle biopsies.

The etiology of cirrhosis was determined by serum hepatitis C virus (HCV)-related cirrhosis. Patients with confirmed liver cirrhosis severity of liver disease was determined in each patient using the combination of clinical, biochemical and virological markers, ultra-

Dyspeptic patients with compensated HCV-related cirrhosis enrolled in an interferon treatment trial were recruited for the present study. The diagnosis of cirrhosis was confirmed by a combination of clinical, biochemical and virological markers, ultrasound imaging and histopathological parameters. The clinical severity of liver disease was determined in each patient using the Child-Pugh's classification. Patients with confirmed liver cirrhosis without ascertained complications were classified as having compensated liver cirrhosis. Patients with uncompensated cirrhosis were excluded from the study because of increased risks of bleeding associated with biopsies of the liver and gastric mucosa. The etiology of cirrhosis was determined by serum hepatitis markers and histopathology features in liver tissue specimens obtained by needle biopsies.

Each patient was interviewed by a physician, and demographic and medical history were recorded. Patients who received bismuth compounds, antisecretory drugs or antibiotics four weeks before upper endoscopy were excluded. Other exclusion criteria included gastrointestinal surgery, regular use of nonsteroidal anti-inflammatory drugs including acetylsalicylic acid, malignancy, severe heart, kidney and lung disease, or prior treatment for H pylori infection.

The diagnosis of peptic ulcer was based on the endoscopic detection of a typical ulcer crater in the stomach or duodenum of 0.5 cm or larger in diameter. H pylori active infection was defined by 13C-urea breath testing according to a standard protocol (9).

Methods

Dyspeptic patients with compensated HCV-related cirrhosis enrolled in an interferon treatment trial were recruited for the present study. The diagnosis of cirrhosis was confirmed by a combination of clinical, biochemical and virological markers, ultrasound imaging and histopathological parameters. The clinical severity of liver disease was determined in each patient using the Child-Pugh's classification. Patients with confirmed liver cirrhosis without ascertained complications were classified as having compensated liver cirrhosis. Patients with uncompensated cirrhosis were excluded from the study because of increased risks of bleeding associated with biopsies of the liver and gastric mucosa. The etiology of cirrhosis was determined by serum hepatitis markers and histopathology features in liver tissue specimens obtained by needle biopsies.

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The diagnosis of peptic ulcer was based on the endoscopic detection of a typical ulcer crater in the stomach or duodenum of 0.5 cm or larger in diameter. H pylori active infection was defined by 13C-urea breath testing according to a standard protocol (9), and/or identification of the organisms on histological examination of gastric mucosal biopsies obtained at the endoscopy. Two biopsies were taken from the antrum, one from the angularis, and one from the gastric corpus for histological examination. Biopsy specimens were immediately fixed in 10% buffered formalin and subsequently stained with hematoxylin and eosin and giemsa to assess for the presence of H pylori.

Variceal size was measured endoscopically by using Beppu's classification subsequently modified by the North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices (NIEC) (10), and the severity of portal hypertensive gastroopathy was graded as mild to severe as described by McCormack et al (11):

- none: normal endoscopic appearance of the gastric mucosa;
- mild: mosaic or snake-skin appearance;
- moderate: presence of erythema; or
- severe: erosive or hemorrhagic gastritis.

Informed consent was obtained from all patients included in the study and the protocol was approved by the Ethics Committee of the Faculty of Medicine, University of Sassari, Italy.

Statistical analysis

The Fisher's Exact test or χ² was used for analysis of categorical data. The T test was used for continuous data. P<0.05 was considered to be statistically significant.

Results

A total of 178 consecutive patients with compensated cirrhosis who met the inclusion criteria were prospectively enrolled in the study (104 men; mean age 60.5±10.5 years). All patients had HCV-related cirrhosis based on the presence of anti-HCV immunoglobulin G and HCV-RNA positivity in the serum. The prevalence of Child-Pugh's class A cirrhosis was 46% (81 of 178). In the remaining patients, a compensated functional class B cirrhosis was observed.

The overall prevalence for H pylori infection was 43% (76 of 178 patients) (Figure 1). There was no significant difference in the prevalence of H pylori infection between men and women (41% versus 44%, respectively). A clear trend of higher prevalence in older patients was observed (Figure 1). The prevalence of H pylori infection was numerically greater among patients with Child's B (45%; 44 of 97) than in patients with Child's A cirrhosis (37%; 30 of 81), although the difference was not statistically significant (P=0.3). No significant association was observed between H pylori infection and the presence or size of esophageal varices.

The frequency of peptic ulcer disease was 8% in the total population and was statistically more prevalent in H pylori-infected cirrhotic patients (eg, 16% [five patients with gastric ulcers, six with duodenal ulcers, and one with both] versus 2% among H pylori uninfected patients [two patients with gastric ulcers] [OR 8; 95% CI 3.6 to 45.4]). Peptic ulcer was more prevalent in patients with severe portal hypertensive gastroopathy (four of 13) compared with patients with mild gastroopathy (six of 89) (31% versus 7%) (Table 1). Eighty-six per cent of all patients with peptic ulcers were positive for H pylori infection (Table 1). Gastric mucosal erosions were detected endoscopically in 36% of the population, with a similar prevalence in patients with and without H pylori infection (39% versus 33%). Erosions were significantly more common in patients

![Figure 1) Prevalence of Helicobacter pylori (Hp) infection by age decades in patients with hepatitis C virus-related compensated cirrhosis](image-url)
with severe (92%) than in patients with mild (47%) portal hypertensive gastropathy (12 of 13 versus 42 of 89, respectively; P=0.006) (Table 1). There was no association between severity of portal hypertension gastropathy and H pylori infection.

DISCUSSION

Cirrhosis represents a late stage of progressive hepatic fibrosis. Generally, cirrhosis is considered to be irreversible in its advanced stages. At this point, the only option may be liver transplantation. Patients with cirrhosis are susceptible to a variety of complications and their life expectancy is markedly reduced. Once a patient develops complications of cirrhosis, they are considered to have decompensated disease. The high morbidity and mortality of cirrhosis is secondary to these devastating complications. The quality of life and survival of cirrhotic patients can be improved by the prevention and treatment of these complications.

Peptic ulcer prevalence has been reported to be higher in patients with cirrhosis than in controls, with an incidence 10-fold greater than the normal population (12), and has been recognized as the cause of 16% of overall upper intestinal hemorrhages in those patients (13). More importantly, bleeding from a peptic lesion is associated with an increased risk of death in cirrhotic patients of fivefold (14); therefore, prevention of bleeding has to be considered in these patients.

The present study endoscopically evaluated the presence of an active peptic ulcer in a large population of dyspeptic cirrhotic patients. Overall, the point prevalence of peptic ulcer observed in our study was in agreement with that reported in previous studies, conducted in the same geographical area, among dyspeptic patients positive for H pylori infection but negative for HCV infection and cirrhosis (15,16). Importantly, in the present study, peptic ulcer was associated more often with H pylori infection (16% versus 2%; OR 8.0). Although peptic ulcer was numerically greater among H pylori-infected patients with congestive gastropathy than in patients without gastropathy (9% versus 4%, respectively), the difference was not statistically significant. Available data on the prevalence of H pylori infection in cirrhotic patients with peptic ulcer, established using serology, range widely from 44% to 95% and from 50% to 87% for duodenal and gastric ulcer, respectively (17). Siringo et al (18) reported a highly significant difference in the prevalence of H pylori infection between cirrhotic patients with and without peptic ulcer disease (95% versus 70%, P=0.0004). In the study by Wu et al (4), the prevalence of H pylori infection was higher in cirrhotic patients with peptic ulcer (79%) than in those without (65%), although the difference did not reach the statistical significance. Moreover, the presence of immunoglobulin G anti-H pylori was found to be a significant independent risk factor for peptic ulcer development in patients with cirrhosis (6). More specifically, when invasive methods such as histology, rapid urease test and culture were used simultaneously to detect the bacteria, the prevalence of H pylori infection was 94% in patients with peptic ulcer disease (19). In our study, H pylori infection was not detected in only one patient with gastric ulcer, using histology and 13C-urea breath testing (Table 1).

Congestive gastropathy is a clinically relevant entity because of its significant risk for both chronic occult and overt bleeding in cirrhotic patients. This gastric manifestation of portal hypertension is present in up to 50% of cirrhotic patients (20), and accounts for one-third of bleeding events in these patients (21). In the present study, the prevalence of H pylori infection was similar in patients with congestive gastropathy compared with patients without (42% versus 46%), as previously demonstrated (22,23), and peptic ulcer disease was slightly more prevalent among H pylori-infected patients with congestive gastropathy than in infected patients without congestive gastropathy. Overall, observations from the literature seem to indicate that congestive gastropathy and H pylori infection are independent factors that may affect the gastric mucosa. A possible synergism between H pylori infection and portal hypertensive gastropathy leading to peptic ulcer disease may be present (17). Factors such as a reduced production of bile salts and the impairment of gastric mucosal defense due to the portal hypertensive gastropathy in cirrhotic patients may allow H pylori to be more aggressive in the stomach and duodenal bulb than in subjects without cirrhosis.

CONCLUSIONS

The clinical relevance of these results would be that dyspeptic patients with HCV-related cirrhosis might benefit from preventive screening and eradication of H pylori, especially those with congestive gastropathy and stigmata of insufficient hemostasis. It has been evaluated that treatment of H pylori infection is more effective than antisecretory noneradicating therapy (with or without long-term maintenance antisecretory therapy) in preventing recurrent bleeding from peptic ulcer (24). The eradication of H pylori may have several theoretical advantages among this population group, including prevention of H pylori-related peptic ulcers and ulcer complications as well as decreasing the burden of dyspeptic symptoms.

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