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Helicobacter pylori infection and the risk of adenocarcinoma of the esophagus

In the recent years, the prevalence of adenocarcinomas of the esophagus has substantially increased. At present its prevalence in the USA is comparable to that of squamous carcinoma (5/100,000 a year). In 80–90% of cases esophageal adenocarcinoma is located in 1/3 of the lower esophagus and is mainly derived from Barrett's esophagus (BE). Barrett's esophagus is defined as the change of the stratified squamous epithelium into the columnar one with intestinal metaplasia. Such a condition may be the complication of gastroesophageal reflux disease (GERD) and is regarded as the precancerous stage. It was estimated that the risk of adenocarcinoma of the esophagus in patients with Barrett's esophagus was 30–125 times higher than in the entire population. The role of *Helicobacter pylori* (Hp) infection in the pathogenesis of gastritis and gastric ulcer disease has been well known and documented. However, its role in the pathogenesis of esophageal reflux disease, its complications, particularly regarding the risk of Barrett's esophagus and adenocarcinoma is still being studied. The relation between Hp infection and BE has been discussed for many years. The importance of the problem is warranted by the wide prevalence of both Hp infection and reflux disease in the population. The first reports about the presence of Hp in the metaplastic epithelium of the esophagus were published in 1991 (1). Evaluating the prevalence of Hp in BE, the authors observed a positive reaction in the esophageal mucosa specimens in 44.3% of patients. No correlation was observed between Hp infection and intensified inflammatory changes. Later, in 1992, L o f f e l d et al., studying Hp in the group of 107 patients with the columnar epithelium in the esophagus, demonstrated that the majority of patients with (+) Hp showed a low degree of colonization in the metaplastic epithelium. The authors presume that Hp in the esophageal mucosa in the columnar epithelium originates from the prepyloric gastric segment. It is likely that Hp does not play any relevant role in the etiology of esophageal inflammatory changes and the development of BE (4).

The similar results were obtained by R i c a u r t e et al. in their prospective study in patients with BE (9). The study involved 73 patients. Hp infection was observed in the esophageal mucosa in 15% and in the gastric mucosa – in 35% of cases. The authors believe that Hp does not play a significant role in the development of BE and that colonization of the metaplastic mucosa by these bacteria reflects their presence in the gastric mucosa. Moreover, studies were performed to answer the question whether Hp, regarded as class I carcinogen in stomach cancer, may contribute to the development of metaplastic epithelium-associated esophageal cancer. W r i g h t et al. demonstrated histologically the presence of Hp in 34% of the BE cases without dysplasia and only in 17% of the patients with dysplastic lesions (dysplastic/malignant cases) (4). No correlation was observed between the presence of Hp and the length of BE, ulcers or strictures and previous anti-reflux surgery. A negative correlation was found between the grade of dysplasia and presence of Hp. These findings allow to put forward a hypothesis about protective effects of Hp against the development of dysplasia in patients with BE.

The relation between Hp and BE was also studied by Quddus et al. (8). Nineteen cases of BE-derived adenocarcinoma were examined for Hp. To detect Hp, the specimens of many tissue blocks were stained with hematoxylin, eosin, by Giemsa method and antibodies against Hp. The specimens were assessed independently by two pathologists. All the three methods of staining did not reveal the presence of Hp in any of the cases examined. According to the authors, neither gastric nor esophageal Hp infection influences the development of adenocarcinoma in BE. The relation between Hp infection and BE-associated adenocarcinoma is unlikely.

The above-mentioned results are questioned by the researchers from Ireland. In order to explain the role of Hp in esophageal diseases, Henihan et al. analysed 141 patients with histologically confirmed pathology of the esophagus (2). The group examined included 82 patients with BE, 19 – with adenocarcinoma of the esophagus originating from the columnar epithelium and 40 – with reflux esophagitis without columnar metaplasia of the esophagus. Hp was detected in 19 patients with BE, however, it was not observed in all the patients with esophageal adenocarcinoma. Hp was detected only in the gastric-type metaplastic areas. The patients from the Barrett's group with symptoms of medium and severe dysplasia did not suffer from Hp infection. These data confirm that the presence of the gastric-type mucosa in the esophagus is a prerequisite for Hp colonization and that Hp may affect the severity of inflammatory changes in the Barrett's epithelium.

The results of studies performed by American and Australian researchers also seem to support the protective effects of Hp infection. Lord et al. studied the prevalence of Hp in the group of 160 patients with BE and evaluated the role of this infection in the development of adenocarcinoma (6). They found out that esophageal Hp infection is rare in patients with BE and adenocarcinoma (positive tests only in 5% of patients). The control patients with endoscopically diagnosed ulcers or inflammatory lesions of the duodenum and stomach showed higher frequency of Hp infection compared to BE. It may be supposed that Hp infection is likely to prevent the development of BE.

Some extremely interesting studies were presented by Weston et al. (12). In the group of 289 individuals the authors evaluated the prevalence of gastric Hp infection in patients with GERD, Barrett's dysplasia and Barrett's adenocarcinoma. It was demonstrated that the frequency of high grade dysplasia in BE and adenocarcinoma was significantly higher in patients without Hp infection. The authors believe that Hp may prevent the development of Barrett's adenocarcinoma. Moreover, the researchers are interested in the role of mutability of Hp strains in complicated reflux disease, particularly in Barrett's esophagus (10). In the group of 251 patients, the frequency of colonization with cag A(+) and cag A(-) Hp strains was studied according to the spectrum of reflux disease, including BE. The prevalence of cag A(+) Hp colonization was found to be significantly higher in controls (44%) and patients with GERD (36%) than in patients with short BE segments (20%) and long BE segments (0%). It was concluded that colonization with cag(+) Hp strain might prevent BE and its malignant complications.

The similar results were reported by Dutch authors (Loffeld et al.), who observed that the patients with reflux inflammation of the esophagus and BE showed a significantly higher frequency of Hp colonization than the controls, which particularly concerned cag A infection. These results suggest that colonization with cag A(+) Hp strains may prevent the development of GERD (5) . The studies involved 736 patients.

Furthermore, some retrospective studies examining the specimens of the gastric and esophageal mucosa in patients with GERD, BE, NUD (non-ulcer dyspepsia) were performed. The percentage of Hp infection showed no differences between the GERD patients with BE (53.3%) and without metaplasia (51.4%) or neoplasia (47.8%), yet was statistically significantly lower compared to the controls with NUD (65.7%). The above studies demonstrated that there was no increased risk of the development of BE or metaplasia in BE among patients with GERD and Hp infection. Since the prevalence of Hp infection is significantly lower in GERD patients than in those with NUD, the protective effects of Hp infection are worth discussing (11).

The relations between the grade and location of gastric inflammatory lesions and Hp infection as well as BE (7) were examined. It was observed that a high percentage of patients with the columnar epithelium in the lower esophageal segment had Hp infection with inflammatory changes present in the whole stomach, however, their activity was low.

In the recent months some studies were published evaluating the effects of Hp infection on the induction of apoptosis in the BE-derived adenocarcinoma cells (3). The authors demonstrated that Hp-induced apoptosis was higher in the BE adenocarcinoma cells than in normal cells of the esophageal epithelium. Apoptosis induced by Hp was primarily dependent on an intact bacterium and the presence of cag A and pic B/cag E gene products. The Fas-caspase cascade may be involved in the Hp-induced apoptosis.

The above mentioned findings confirm the protective effects of Hp infection in BE. Eradication of Hp is not recommended at any stage of esophageal reflux disease. Despite numerous studies some doubts concerning the relation between Hp infection and BE are still to be explained.

CONCLUSIONS

1. The presence of the gastric-type mucosa is a prerequisite of *Helicobacter pylori* colonization.

2. *Helicobacter pylori* infection may significantly affect the severity of inflam--matory changes in the esophagus.

3. Patients with GERD symptoms and concomitant Hp infection show no increased risk of the development of Barrett's esophagus and esophageal adenocarcinoma.

4. The cag A(+) Hp infection is thought to be a "protective factor" for the development of Barrett's esophagus and its complications.

5. Antineoplastic effects of Hp may result from the activation of apoptosis in the esophageal adenocarcinoma cells.

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SUMMARY

In the recent years, the prevalence of adenocarcinomas of the esophagus has substantially increased. At present its prevalence in the USA is comparable to that of squamous carcinoma (5/100,000 a year). In 80–90% of cases esophageal adenocarcinoma is located in 1/3 of the lower esophagus and is mainly derived from Barrett's esophagus (BE). The role of *Helicobacter pylori* (Hp) infection in the pathogenesis of gastritis and gastric ulcer disease has been well known and documented. However, its role in the pathogenesis of esophageal reflux disease, its complications, particularly regarding the risk of Barrett's esophagus and adenocarcinoma is still being studied. The relation between Hp infection and BE has been discussed for many years. The importance of the problem is warranted by the wide prevalence of both Hp infection and reflux disease in the population. The above mentioned findings confirm the protective effects of Hp infection in BE. Despite numerous studies some doubts concerning the relations between Hp infection and BE are still to be explained.

Infekcja *Helicobacter pylori* a ryzyko gruczolakoraka przełyku

W ostatnich latach znacznie zwiększyło się występowanie gruczoralokoraka przełyku i obecnie w USA osiągnęło częstość porównywalną z rakiem płaskonabłonkowym (5/100000 na rok). Gruczolakorak przełyku jest umiejscowiony w 80–90% przypadków w 1/3 dolnej części przełyku i powstaje głównie na podłożu przełyku Barretta (BE). Rola infekcji *Helicobacter pylori* (Hp) w patogenezie zapaleń śluzówki żołądka i chorobie wrzodowej została dobrze poznana i udokumentowana. Natomiast rola tej bakterii w patogenezie choroby refluksowej przełyku, jej powikłań, szczególnie w aspekcie ryzyka rozwoju przełyku Barretta i raka gruczołowego, wciąż jest przedmiotem wielu badań. Od lat toczy się dyskusja na temat związku między obecnością infekcji Hp a występowaniem BE. Wagę problemu uzasadnia szerokie rozpowszechnienie w populacji zarówno infekcji Hp, jak i choroby refluksowej. Niektóre doniesienia potwierdzają korzystne działanie infekcji Hp w BE. Mimo wielu badań nie wszystkie wątpliwości dotyczące związku między infekcją Hp i BE zostały wyjaśnione. Wnioski: 1. Warunkiem kolonizacji *Helicobacter pylori* w przełyku jest obecność śluzówki typu żołądkowego. 2. Infekcja *Helicobacter pylori* może wywierać istotny wpływ na stopień nasilenia zmian zapalnych w przełyku. 3. Pacjenci z objawami GERD i współistniejącym zakażeniem *Helicobacter pylori* nie mają zwiększonego ryzyka rozwoju przełyku Barretta i gruczolakoraka przełyku. 4. Uważa się, że infekcja szczepu *Helicobacter pylori* cag A(+) stanowi czynnik chroniący przed wystąpieniem przełyku Barretta i jego powikłań. 5. Przeciwnowotworowe oddziaływanie *Helicobacter pylori* może wynikać z aktywacji apoptozy w komórkach gruczolakoraka przełyku.