PŮVODNÍ PRÁCE

Histopathologic Changes in Gastroesophageal Reflux Disease. A Study of 126 Bioptic and Autoptic Cases

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Summary

The histologic diagnosis of reflux esophagitis is still complicated by the lack of a consensus opinion on what is the normal mucosa in the area of the gastroesophageal junction (GEJ). Most authors consider GEJ as the junction between the squamous and the cardiac epithelium. The cardiac mucosa is composed of mucinous or mixed mucinous-oxyntic glands. These glands are in fact indistinguishable from metaplastic mucosa that arises in the distal esophagus in consequence of gastroesophageal reflux (GER). The cardiac mucosa shows invariably chronic inflammatory changes referred to as "carditis". The cause of "carditis" is GER and/or *Helicobacter pylori* (HP) infection.
In our series of 120 endoscopic biopsies of the GEJ and distal esophagus the cardia type mucosa (CM) was always present. In 15 cases, it was accompanied by oxyntocardiac mucosa. Both mucosa types showed chronic inflammation that is after exclusion of HP infection regarded as a strong diagnostic sign of the gastroesophageal reflux disease (GERD). In two cases with clinical symptoms of GERD, a few HP were found on the CM. Therefore we diagnosed them as GERD with secondary HP infection. In 17 cases, CM displayed intestinal metaplasia (IM) predominantly of incomplete type and no dysplasia. This IM expressed MUC6 in the glandular zone of the mucosa like it did in the neighboring glands, whereas in the surface and foveolar epithelium the MUC6 was negative or only slightly and focally positive. On the other hand, IM in the surface and foveolar epithelium was reactive for MUC5AC. The positivity and distribution of CK7 and CK20 was very similar in the Barrett's mucosa, cardiac mucosa and antral mucosa.
In one specimen of esophagus resected for adenocarcinoma, CM with incomplete IM was found in the vicinity of the tumor. Squamous metaplastic epithelium was often seen near the orifices of submucosal esophageal glands in these areas, indicating the metaplastic nature of the glandular mucosa in the distal esophagus. In the GEJ of 5 autopsy cases of children with spastic quadriplegia (age range 7-10 years) CM in a short segment (0.5-3 mm in length), probably of metaplastic origin was identified, showing chronic inactive inflammation.

Key words: gastroesophageal junction – gastroesophageal reflux disease – gastric cardia – carditis – metaplasia of the esophagus – intestinal metaplasia

Souhrn

Histopatologické změny u gastroezofageální refluxní nemoci. Studie souboru 126 bioptických a autoptických případů

Histologickou diagnózu refluxní ezofagitidy (RE) komplikuje nejednotný názor na typy sliznic v oblasti gastroezofageální junkce (GEJ). V současné době převládá názor, že v oblasti GEJ přechází dlaždicový epitel jícnu do žlazové sliznice kardie žaludku. Sliznice kardie je tvořena hlenovými nebo smíšenými hlenovými/oxyntickými žlázkami, které jsou neodlišitelné od metaplastické sliznice, vznikající v distálním jícnu při gastroezofageálním refluxu (GER). Ve žlazové sliznici se pravidelně nacházejí chronické zánětlivé změny označované jako „carditis". Jejich příčinou je GER a/nebo infekce *Helicobacter pylori* (Hp). V naší sestavě 120 biopsií z oblasti GEJ a distálního jícnu byla ve všech zachycena sliznice typu kardie (CM), v 15 případech současně s oxyntokardiální sliznicí. V obou typech sliznic byl chronický neaktivní zánět, který se po vyloučení infekce Hp všeobecně považuje za diagnostický pro RE. U dvou nemocných se symptomatologií GER byla na povrchu CM řídká kolonizace Hp. Nález jsme hodnotili jako RE se superponovanou infekcí Hp. V 17 případech byla v CM intestinální metaplazie (IM) převážně nekompletního typu bez dysplazie. Intestinální metaplastický epitel exprimoval ve žlázové zoně – podobně jako okolní žlazky – mucin MUC6, zatímco v povrchovém a foveolárním epitelu byl MUC6

negativní nebo vykazoval jen slabou ložiskovou pozitivitu. V povrchovém a foveolárním epitelu byl intestinální epitel naopak pozitivní v barvení MUC5AC. Imunohistochemické vyšetření prokázalo v CM, Barrettově jícnu a v antrální sliznici shodnou lokalizaci cytokeratinů CK7/CK20. V resekovaném jícnu pro adenokarcinom byla v okolí nádoru CM s nekompletní IM. Pod sliznicí se nacházely submukózní žlazky jícnu a v okolí jejich ústí překrývaly žlazovou sliznici ostrůvky dlaždicového epitelu. Přítomnost submukózních žlazek svědčí pro žlázovou metaplazii sliznice v distálním jícnu. V nekroptických jícnech 5 dětí ve věku 7–10 let se spastickou kvadruplegií byla u všech v GEJ zánětlivě změněná CM v délce 0,5–3mm, pravděpodobně metaplastického původu.

Klíčová slova: gastroezofageální junkce – refluxní ezofagitida – kardie žaludku – carditis – metaplazie sliznice jícnu – intestinální metaplazie

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The histologic features of the gastroesophageal junction (GEJ) are still controversial. In "normal" individuals the GEJ corresponds histologically to the squamocolumnar junction or Z line, i. e. the transition between the esophageal squamous epithelium and the gastric cardia. The length of the cardiac mucosa with pure mucous glands or with a mixture of mucous/oxyntic glands is variable, ranging from 1.0 to 4.0 mm (8, 12-14, 23). In addition, the type and length of the epithelium within the true gastric cardia may vary in different portions of the circumference of the cardia within individual patients (12, 20, 22, 23, 27). The presence of the true gastric cardia (mean length of 1.0 mm) was also documented both in autopsy (8, 20) and biopsy specimens of pediatric patients (12). Until recently, it was believed that the distal 1- 2 cm of esophagus is normally lined by mucinous columnar epithelium similar in appearance to the cardiac mucosa serving from the functional point of view as a "buffer zone" between the esophagus and the stomach (12, 13, 27). However, recent data strongly suggest that mucinous columnar epithelium above the anatomic GEJ is abnormal, namely, metaplastic in origin (1-3, 6, 22, 27). As it is difficult to distinguish the true gastric cardia from the metaplastic columnar epithelium in the distal esophagus, there are problems in the diagnosis of gastroesophageal reflux disease (GERD) and Barrett's esophagus (BE).

In this study, we present the features of GEJ in a series of 120 endoscopic biopsies from GEJ, one resectate of the esophagus, and 5 autopsy specimens of the distal esophagus of children.

Materials and Methods

We examined 120 endoscopic biopsies from the GEJ and distal esophagus. Two to 4 specimens were obtained in every case. 86 patients were males and 34 were females (age range 43-57 years, average 52 years) with clinical symptoms of GERD (102 patients, i.e. 85%) and/or hiatal hernia (18 patients, i.e. 15%). In addition, we examine one resectate of the esophagus with adenocarcinoma in a 58-year-old male, and 5 autoptic specimens of the esophagus from 7- to 10-year-old boys with serious perinatal hypoxic-anoxic injury of the brain resulting in spastic quadriplegia.

In the esophageal resectate and in all autoptic specimens, the whole circumference of the distal part of the esophagus in the length of 2 cm together with the adjacent gastric wall was cut longitudinally and processed in 5 to 6 blocks. All specimens were fixed in 10% formalin and embedded in paraffin. The sections were stained with HE, PAS, Alcian blue (pH 2.5) and silver-impregnated according to Warthin-Starry. Ten bioptic specimens of cardia type mucosa (CM), 5 samples of BE and 10 specimens of antral mucosa were studied immunohistochemically using antibodies to the following antigens: MUC 5AC (CLH2, MW, 1:400, Novocastra), MUC6 (CLH5, MW, 1:400, Novocastra), CK7 (OV-TL12/30, MW, 1:200, DakoCytomation), CK 20 (KS20.8, MW,1:100, DakoCytomation). The primary antibodies were visualised using streptavidin-biotin-peroxidase complex (DakoCytomation).

Results

In all biopsy specimens, both squamous cell and glandular mucosa were seen. These mucosa types were found either apart in isolated fragments, or together in a single tissue fragment in which a transition between the mucosa types could be identified. The squamous epithelium of the esophagus showed non-specific reactive changes (basal cell hyperplasia and an extension of the connective tissue papillae of the lamina propria more than two-thirds of the distance to the surface) and a mild lymphoplasmacytic infiltration in the lamina propria (less than 12 lymphocytes/plasmacytes per HPF). The glandular mucosa contained mucous glands consistent with CM. In 15 cases, CM was accompanied by oxyntocardiac mucosa in which typical parietal cells were found within otherwise mucous glands. In all cases, a chronic inactive inflammation was seen in both