Esophageal dysplasia and adenocarcinoma: a study with double immunostaining for intestinal and gastric markers

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SUMMARY

Columnar lined esophagus is a complication of long term gastroesophageal reflux disease and the main precursor of esophageal adenocarcinoma. Incomplete intestinal metaplasia in reflux esophagitis represents one of the most important risk factors for neoplastic transformation through the metaplasia–dysplasia–adenocarcinoma sequence. However, recent studies suggest that cardiac type mucosa also shows molecular abnormalities which are similar to those of incomplete intestinal metaplasia. Immunohistochemically, three types of esophageal dysplasia and adenocarcinoma are recognized: adenomatous-intestinal, hybrid/mixed and foveolar gastric types. We are interested in the phenotypes of these dysplasias and adenocarcinomas, especially in the possible relationship between them. For this reason, we evaluated the immunohistochemical expression of intestinal and gastric markers in a series of 30 cases of esophageal high-grade dysplasia (high-grade intraepithelial neoplasia) and of 70 adenocarcinomas. For immunohistochemical classification, we used double immunohistochemical reactions CDX2/MUC5AC and CDX2/MUC6, respectively. In cases of incomplete intestinal metaplasia, hybrid/mixed high-grade dysplasia and hybrid/mixed adenocarcinoma, we found the expression of gastric mucins MUC5AC and MUC6 only in cells with intestinal differentiation (with nuclear positivity for CDX2). The double immunostaining excluded the presence of the cells with "pure" foveolar gastric phenotype in hybrid lesions. Thus, the hybrid category actually represents the intestinal type dysplasia/adenocarcinoma (which is known to have a better prognosis than the foveolar gastric type).

Keywords: immunohistochemistry – double immunostaining **–** reflux esophagitis – Barrett esophagus – esophageal dysplasia – esophageal adenocarcinoma

Dysplazie a adenokarcinom jícnu: studie dvojité exprese intestinálních a gastrických markerů

SOUHRN

Kolumnární epitel jícnu je komplikací refluxní ezofagitidy a hlavním prekurzorem adenokarcinomu jícnu. Nejdůležitějším rizikovým faktorem pro vznik adenokarcinomu jícnu u refluxní ezofagitidy je nekompletní intestinální metaplazie s postupným vývojem metaplazie - dysplazie - adenokarcinom. Podle nových studií vykazuje ale podobné molekulární odchylky jako nekompletní intestinální metaplazie také sliznice typu kardie. Z tohoto důvodu se v současné době imunohistochemicky rozlišují 3 typy dysplazie a adenokarcinomu jícnu: adenomatózní - intestinální, hybridní/smíšený a foveolární gastrický. Abychom si ověřili jednotlivé typy dysplazie a adenokarcinomu jícnu a jejich vzájemné vztahy, vyšetřili jsme imunohistochemicky intestinální a žaludeční markery v sestavě 30 high-grade dysplazií a 70 adenokarcinomů. Pro imunohistochemickou klasifikaci jsme použili dvojitou (double) reakci CDX2/MUC5AC a CDX2/MUC6. Ve všech případech nekompletní intestinální metaplazie, hybridní/smíšené high-grade dysplazie a hybridního/smíšeného adenokarcinomu byla touto metodou prokázána exprese gastrických hlenů MUC5AC a MUC6 pouze v buňkách s intestinální diferenciací (jadernou pozitivitou CDX2). Dvojité barvení vyloučilo přítomnost buněk„čistého" gastrického fenotypu v hybridních lézích. Z našich nálezů vyplývá, že kategorie hybridní představuje ve skutečnosti dysplazii a adenokarcinom intestinálního typu.

Klíčová slova: imunohistochemie – dvojitá exprese – refluxní ezofagitida – Barrettův jícen – dysplazie jícnu – adenokarcinom jícnu

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Reflux esophagitis with columnar lined esophagus is a complication of long-term gastroesophageal reflux disease and represents the main precursor of esophageal adenocarcinoma (1-4). Three epithelial types, cardiac, oxyntocardiac and intestinal are recognized to constitute gastroesophageal reflux disease often in a specific direction from distal to proximal in the esophagus (2,3,5,6). The presence of intestinal metaplasia (IM) has a greater impact on prognosis (2,3). On the basis of morphology and mucin production, the following immunohistochemical classification of IM was proposed: 1. the mixed intestinal and gastric type, i.e. incomplete IM with intestinal epithelium, producing gastric mucins and generally lacking an absorptive epithelium, and 2. the purely intestinal type, i.e. complete IM with the presence of goblet cells, absorptive cells, neuroendocrine cells and Paneth cells (7-11). Recently, it has been suggested that incomplete IM which produces gastric mucins represents an initial, immature, and genetically and chromosomally unstable stage (11) with increased proliferation activity (9). This incomplete IM may either undergo maturation into complete non proliferative IM or it persists and progresses to dysplasia and adenocarcinoma (10-18). The esophageal dysplasia and adenocarcinoma are currently classified into the following three types: 1. adenomatous/intestinal, 2. hybrid/mixed, 3. foveolar gastric (19). This classification is based on the presence of intestinal and/or gastric foveolar differentiation. It is suggested that intestinal differentiation means a better prognosis in comparison with foveolar gastric differentiation (8,15,16), and

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