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MORPHOLOGY OF THE MAJOR DUODENAL PAPILLA CARCINOMAS

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Abstract

80 cases of biopsy and 25 samples of resectable carcinomas of the major duodenal papilla, pancreatic head and common bile duct, also known as periampullary, were examined. Histological, histochemical and immunohistochemical peculiarities of pancreatobiliary and intestinal types of cancer were identified. In addition, there were distinguished the differential diagnostic criteria between the major duodenal papilla carcinomas and tumor-like ampullary lesions. Immunophenotype of ductal carcinomas of papilla of Vater is characterized by: CK-7 +, CK-20 – , CEA +, CA 19-9 +. But CEA and CA 19-9 expression has no independent significance for diagnosing histological types of carcinomas

Key words: carcinoma of major duodenal papilla, biopsy, Cytokeratin 7, Cytokeratin 8, Cytokeratin 14, Cytokeratin 20.

Introduction

Today the tumours of the periampullary region are a great problem in abdominal surgery which is caused by diagnostic difficulties, high frequency non-operative stages and numerous technical complexities in performing operations. Papilla of Vater is a key anatomical structure in the place of fusion bile and pancreatic ducts. It is also often an object for surgical and endoscopical manipulation, sometimes representing no less danger than the underlying disease [1]. Most of these tumours are well-differentiated adenocarcinomas which arise from the ampulla of Vater and account for a small percentage of all gastrointestinal malignancies with rates estimated to be in the range of 0.5% [2]. Papilla of Vater is a specific formation due to its anatomical, histological structure and histogenesis, which shows itself in clinically significant features of differentiation of tumour elements. It is proved by histological and histochemical peculiarities as well as by cyto- and molecular genetic ones of tumour cells [3-7]. There exist technical difficulties connected with taking biopsy of the papilla of Vater due to its complex anatomical structure [8].

It results in diagnostic problems because these cases are found comparatively rarely in general surgical and oncological hospitals.

Materials and Methods

The research material is presented by 80 biopsies of the major duodenal papilla and 25 organ complexes after pancreatoduodenectomy (50 male and 55 female specimens). Sex, age, clinical data, pathological and clinical diagnoses are taken into consideration. The age range was from 31 to 84 years (mean 66.9±4.5 in biopsy group and 65.1±3.9 in group of operative material). Significant differences between the sexes were not found. Hematoxylin and eosin, PAS-reaction with alcian blue staining were performed. The expression of Pan-Cytokeratin (Dako; clone AE1/AE3, clone MNF-116), Cytokeratin 7 (CK 7, Dako; clone OV-TL 12/30), Cytokeratin 8 (CK 8; Dako; clone 35βH11), Cytokeratin 14 (CK 14; Biogenex; clone LL 003), Cytokeratin 20 (CK 20; Dako; clone Ks 20.8), Carcinoembryonic antigen (CEA; Dako), cancer antigen 19-9 (CA 19-9; Biogenex), chromogranin A (Dako), Ki 67 (Dako; clone MIB-1), p53 (Dako; clone DO-7), smooth muscle actin (Dako; clone 1A4) was examined. We used the protocol of Heat Induced Epitope Retrieval in EDTA Buffer (pH=9.0). The visualization was down with the high-sensitive polymeric system "Biogenex" followed by hematoxylin nuclei extra staining according to the standard methods. The microscope "Micmed-6" with camera "DCM-300" and "WCIF-Image J-1.341" were used for morphometrical investigation. Statistic data were analyzed by MS Excel with the identification of $[khi]^2$ and Student's test.

Main Part

The analysis follow-up of the study showed that the frequency of papillary carcinomas does not depend on the sex in age groups. A maximum number of cancer cases were found at the age of 50-70 (55.9%) with gradual decreasing in the next decade of life (40%). A minimum of such cases was discovered at the age of 31-40 and more than 80. Cancer of papilla of Vater was clinically suggested in 76 cases out of the total number of 80. In 4 cases clinically benign lesions were diagnosed and completely confirmed histologically. In the group with the periampullary carcinomas the results were quite different.

The cancer confirmation was only received in 17.9% of cases. The acute and chronic papillitis was found in 41.1% of cases. 10.7% of cases presented adenomas and adenomatous lesions. 19.6% of cases were diagnosed as non-tumour diseases or the material was non-informative. After the complete examination of 80 cases 10.7% of them remained under suspicion of malignant tumour.

Thus, during the first biopsies examination the diagnoses of major duodenal papilla cancer was given in 28.6% of cases. This result objectively reflects the sensitivity of the investigation of papillary biopsies without preliminary papillotomy. As the literature reports, the sensitivity of such procedure makes only 21% after histological examination [9]. Papillotomy being down increases its sensitivity up to 37% only.

What makes diagnosing much more difficult is artifacts, cell deformation after electrocoagulation with the cell stretching along the electric current line being the most frequent among them. Following them there are artifacts of mechanical compression, fragmentation and splitting of structures they create a false image of cell atypia, pseudoinvasion and stromal edema. Cystic lesions of the glands in the ostium area of major duodenal papilla can mimic the glandular atypia. In diagnosing adenomas of papilla of Vater with dysplasia it is necessary to be careful. According to the C.D. Heidecke's research out of 32 cases of pre-operation adenomas of major duodenal papilla diagnosed after the postoperative histological examination was the following: 14 cases of adenoma, 9 cases of carcinomas, 3 cases lower-grade dysplasia and 6 cases high-grade dysplasia. The significance of adenomas as pre-cancer lesions is not evident. In cases of major duodenal papilla cancer adenomatous changes are found in between 20 to 91%. [10, 11].

In the material understudy highly-differentiated adenocarcinoma of papilla of Vater was identified in 12 years following the adenoma resection of major duodenal papilla. Under the retrospective examination of the material the increasing grade of atypia was insignificant. However, in adenocarcinoma there were seen high expression of CEA and high proliferative activity in accordance with Ki67-positive cells equal to 31.5% (in the original material the latter was 12.3%; $p<0.05$).

24 cases with a proved papilla of Vater cancer underwent a thorough examination. A pancreatobiliary type of cancer was identified in 62.5% of cases and intestinal type – in 37.5%. Highly- and well-differentiated carcinomas significantly more often were observed in an intestinal type group (80% v.s. 34.4%; $p<0.05$). The intestinal subtype of cancer is associated with a better prognosis as compared with carcinomas arising from the distal bile duct or pancreas [12]. The origin of ampullary adenocarcinomas can be difficult to distinguish. Two distinct pathological subtypes have been identified – one that arises from the intestinal epithelium or one that arises from pancreatobiliary epithelium [13].

The last 2 variants are extremely rare. The first 3 variants are hard to differentiated histologically and immunohistochemically as they are equal clinically, being the place of origin for pancreatobiliary type carcinomas.

Pancreas, papilla of Vater and bile duct cancer makes one immunophenotype claster in accordance with cytokeratines and mucines expression [14]. Morphogenesis of tumour lesions of the papilla of Vater connected with pancreatic heterotopia is not yet studied completely [15].

The recent literature reports inform of such 13 cancer cases. The tumour size varied from 1 to 3 cm. A complete variant of pancreatic heterotopia was present in 3 cases. On the bases of CK-7 expression and absence of CK-20 the authors came to the conclusion that these tumours are closely related with pancreatic heterotopia and hyperplasia of small bile ducts [16].

Histochemical features and immunophenotype of major duodenal papilla carcinomas determined by as, are presented in the following chart.

Table 1: Immunophenotype of major duodenal papilla carcinomas.

Type	Frequency of positive cases (number and %)					
	CK7	CK8	CK14	CK20	CEA	CA19-9
Intestinal type	3/15 (20%)	15/15 (100%)	0/15 (0%)	13/15 (86.7%)	15/15 (100%)	15/15 (100%)
Pancreatobiliary type	9/9 (100%)	9/9 (100%)	0/9 (0%)	2/9 (22.2%)	7/9 (77.7%)	8/9 (88.9%)

CK-8 expression is positive in all carcinomas of papilla of Vater independent of its histological type. Such reaction being more evident in epithelium than in glands of papilla. CEA expression was discovered by as in malignant epithelium only.

It was combined with high expression of Ki67 and p53. CEA, Ki67, p53 expression is significant for differential diagnosing between malignant tumours and adenomatous lesions of papilla of Vater. Appearing focal CK-20 expression among predominant CK-7 positive cells of ductal epithelium is typical for dysplastic lesions of lining epithelium and glands of major duodenal papilla nearby malignant tumour. Ductal epithelium alcyan blue stain mucin secretion is also typical for malignant epithelium.

In general, immunophenotype of ductal carcinomas of papilla of Vater is characterized by: CK-7 +, CK-20 – , CEA +, CA 19-9 +. But CEA and CA 19-9 expression has no independent significance for diagnosing histological types of carcinomas ($p>0.05$). Besides, chromogranin-A positive endocrinocytes is the main characteristics of intestinal type cancer of papilla of Vater. On average, more than 3 positive cells were seen one glandular structure or crypt. Typical pictures of periampullary carcinomas are presented in figures 1-4.

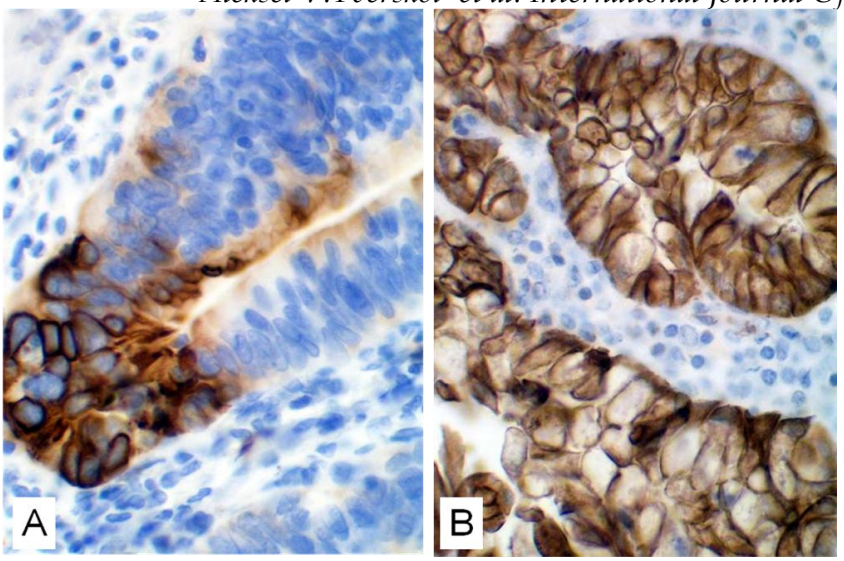

Figure 1. CK20 positive reaction in dysplastic epithelium of common channel (A) and in an intestinal carcinoma of papilla of Vater (B) (×400).

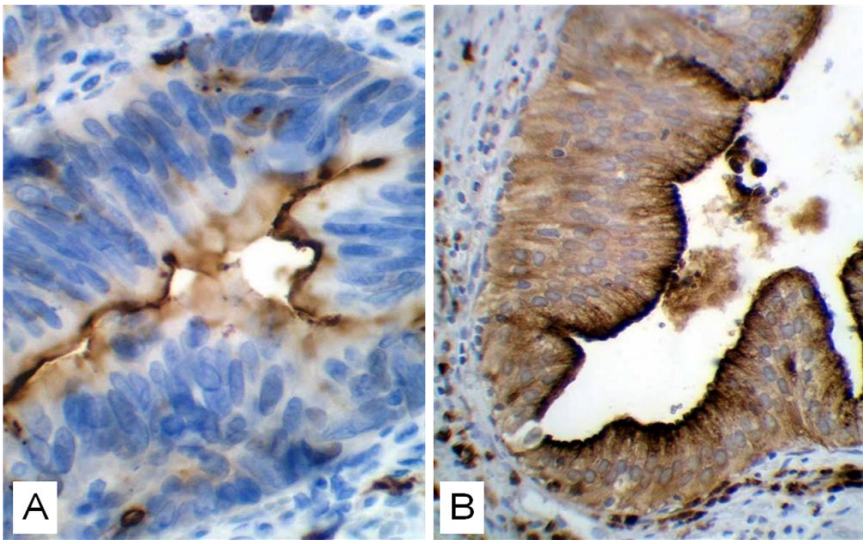

Figure 2. CEA expression in dysplastic epithelium of common channel (A) and in an intestinal carcinoma of papilla of Vater (B) (×400).

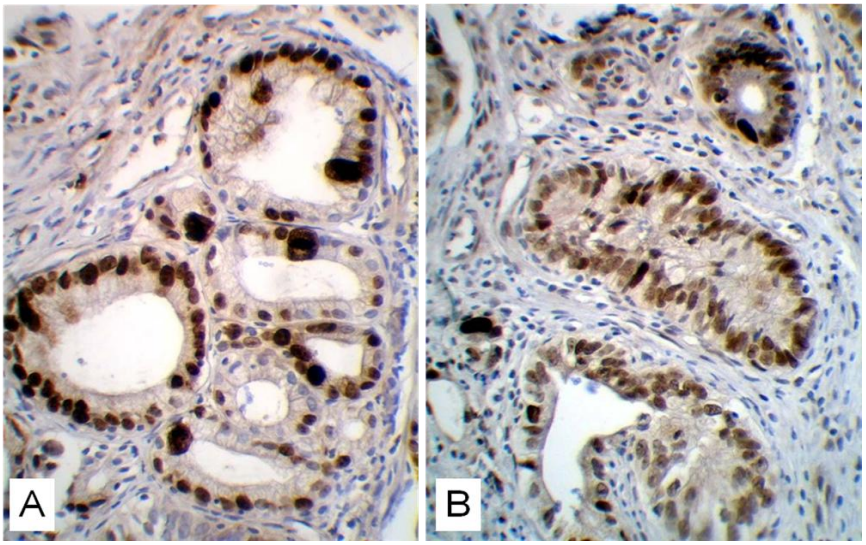

Figure 3. Ki67 (A; >30%) and p53 (B) expression in pancreatobiliary carcinoma of papilla of Vater (×400).

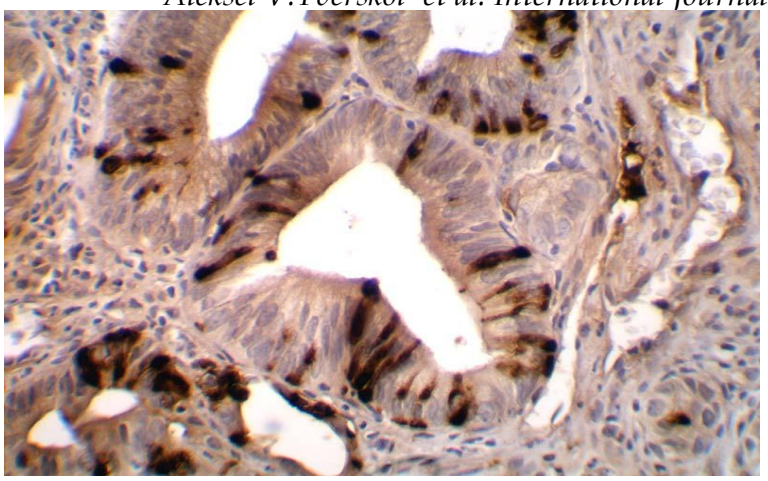

Figure 4. Chromogranon-A positive endocrinocytes in the intestinal type carcinoma of papilla of Vater (×400).

Conclusion

While diagnosing major periampullary carcinomas low sensitivity of routine endoscopic biopsy must be taken into account. Endoscopic biopsy must be performed after papillotomy with taking the material from common channel of hepatopancreatic ampulla closest to common bile duct, pancreatic duct and from duodenal mucosa. CEA, Ki67 and p53 expression is an additional criterium for differential diagnosing between carcinomas and adenomas with dysplasia. It is necessary to identify the type of carcinomas for the following therapy or/and surgery strategy.

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