Gastric-foveolar variant of intraductal papillary mucinous neoplasm of the pancreas associated with invasive tubular adenocarcinoma. Case report and short review of the literature

Wariant żołądkowo-dołeczkowy wewnątrzprzewodowego brodawkowatego nowotworu śluzowego trzustki związany z naciekającym rakiem cewkowym. Opis przypadku i krótki przegląd piśmiennictwa

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Słowa kluczowe: wewnątrzprzewodowy brodawkowaty nowotwór śluzowy, rak trzustki, trzustka.

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Abstract

Intraductal papillary mucinous neoplasms of the pancreas (IPMN) are relatively rare, mucin-producing pancreatic neoplasms that are visible grossly within the pancreatic ductal system and usually form papillary structures. Four main directions of differentiation of IPMN are described: intestinal, pancreaticobiliary, oncocytic and gastric-foveolar (GF-IPMN). We report a histopathological and immunohistochemical study of GF-IPMN which involved the main pancreatic duct and progressed to invasive carcinoma. The presented case of invasive carcinoma derived from IPMN indicates that the dichotomous model of IPMN progression (intestinal pathway or pancreaticobiliary pathway) is inadequate in some IPMN. Additionally, we describe the issues of GF-IPMN epidemiology, molecular characteristics and differential diagnostics.

Streszczenie

Wewnątrzprzewodowe brodawkowate nowotwory śluzowe trzustki (*intraductal papillary mucinous neoplasms* – IPMN) są względnie rzadkimi nowotworami produkującymi śluz, widocznymi makroskopowo w obrębie przewodów trzustkowych, które zwykle tworzą struktury brodawkowate. Opisano 4 główne kierunki różnicowania IPMN – jelitowy, trzustkowo-żółciowy, onkocytarny i żołądkowo-dołeczkowy. W pracy opisano wyniki histopatologicznej i immunohistochemicznej analizy przypadku wariantu żołądkowo-dołeczkowego IPMN zajmującego główny przewód trzustkowy i dającego początek naciekającemu rakowi cewkowemu. Przedstawiony przypadek naciekającego cewkowego raka trzustki wywodzącego się z IPMN wskazuje, że dychotomiczny model progresji IPMN (oparty na drodze transformacji *jelitowej* i *trzustkowo-żółciowej*) w niektórych przypadkach IPMN nie jest odpowiedni. W pracy zaprezentowano zagadnienia dotyczące epidemiologii, charakterystyki molekularnej oraz diagnostyki różnicowej wariantu żołądkowo-dołeczkowego IPMN.

Introduction

According to the recent American Forces Institute of Pathology (AFIP) definition, intraductal papillary mucinous neoplasms of the pancreas (IPMN) are "grossly visible, mucin-producing epithelial neoplasms, that grow within the main pancreatic duct or its branches, and often, although not always, have a papillary architecture" [1]. IPMN make up less than 5% of pancreatic neoplasms [2, 3].

Non-invasive IPMN may be further classified based on the degree of cytoarchitectural dysplasia into IPMN with low-grade (adenoma), moderate-grade (borderline malignancy) and high-grade dysplasia (carcinoma). In one third of IPMN cases invasive carcinoma of the pancreas derived from IPMN is observed [1, 3-10].

In the majority of cases, invasive carcinoma associated with IPMN has one of two histopathological patterns: tubular (or conventional, or not-otherwise-specified)

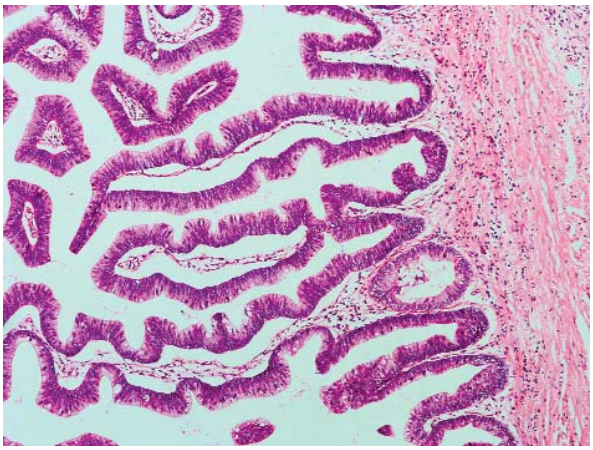

Fig. 1. Intraductal papillary mucinous neoplasm of the pancreas (intestinal type). Magn. 100×
Ryc. 1. *Wewnątrzprzewodowy brodawkowy nowotwór śluzowy trzustki (wariant jelitowy). Powiększenie 100×*

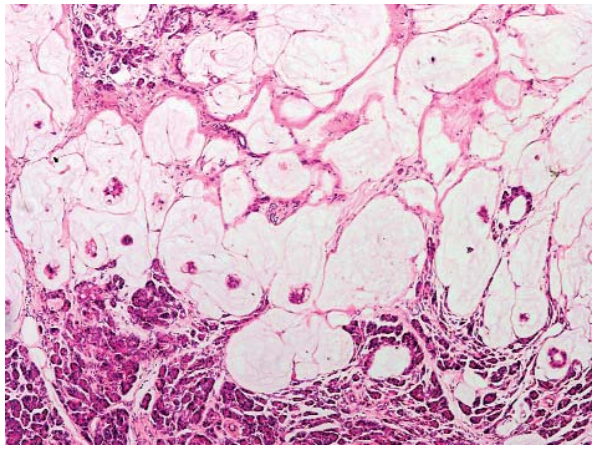

Fig. 2. Colloid (mucinous noncystic) carcinoma. Magn. 100×
Ryc. 2. *Śluzowy nietorbielowaty rak trzustki. Powiększenie 100×*

pattern and colloid (or mucinous noncystic, or muconodular) pattern. In more than 90% of cases, colloid carcinoma of the pancreas is derived from IPMN, and only a few pancreatic neoplasms composed of extensive pools of extracellular mucin with floating neoplastic cells are not associated with IPMN. However, the minority of tubular carcinomas of the pancreas derive from IPMN, because they usually arise from pancreatic intraepithelial neoplasia (PanIN). There are no morphological differences between invasive tubular carcinoma derived from PanIN and invasive tubular carcinoma derived from IPMN, although there are some differences in molecular characteristics and long-term prognosis between these two entities [1, 3, 4, 8, 10-15].

Many different genetic mechanisms related to the development and progression of IPMN and PanIN have been described [16-18]. The role of suppressor genes *TP53* and *CDKN2A/INK4A* and their products (p53 and $p16^{INK4A}$, respectively) as well as proliferation antigens (Ki-67) and cell-cycle proteins (cyclin D1) in pancreatic carcinogenesis is clearly stated [16-18].

In 1999 Yonezawa et al. proposed a new histopathological classification for IPMN [19]. According to this (with some subsequent modifications) IPMN may be classified into four subtypes based on four possible directions of differentiation. Intestinal-type IPMN (I-IPMN, villous-dark cell type (Fig. 1), are composed of tall, dark eosinophilic, mucin-producing columnar cells with pseudostratified oval or spindle nuclei, and form long papillae, similarly to colorectal villous adenoma. They are typically MUC2 and MUC5AC positive and MUC1 negative and may progress to

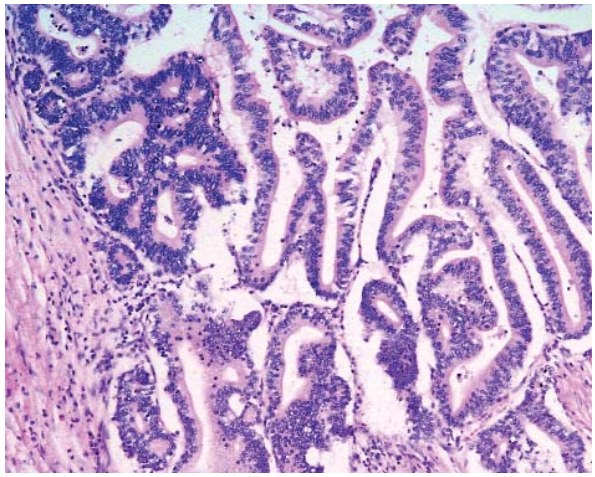

Fig. 3. Intraductal papillary mucinous neoplasm of the pancreas (pancreaticobiliary type). Magn. 100×
Ryc. 3. *Wewnątrzprzewodowy brodawkowaty nowotwór śluzowy trzustki (wariant trzustkowo-żółciowy). Powiększenie 100×*

colloid carcinomas (Fig. 2). Pancreatobiliary-type IPMN (PB-IPMN, compact cell type, Fig. 3) are formed of cuboidal cells, which are usually characterized by higher grade of cytoarchitectural atypia than I-IPMN, and have round nuclei with a single prominent nucleolus. They form complex, often cribriform or branching papillae, usually express MUC1 and MUC5A (but not MUC2) and often progress to tubular carcinoma. Oncocytic IPMN are characterized by

complex papillae composed of oxyphilic cells and are often described as a histopathological entity separate from IPMN. They express MUC1 and (focally) MUC2 and give rise to invasive oncocytic carcinomas [1, 3-7, 10, 11, 13, 14, 19-25].

The neoplastic cells in gastric-foveolar-type IPMN (GF-IPMN, papillary clear cell type, clear cell type or null-type IPMN) are slightly acidophilic (eosinophilic) columnar or cuboidal cells. They have abundant cytoplasmic, basally oriented nuclei and supranuclear mucin and they resemble the cells of the surface epithelium and pits of the stomach [26]. In the majority of cases, they may be described as IPMN with low-grade dysplasia. They usually involve the secondary branches of the main pancreatic duct (branch-duct-type IPMN). They are typically MUC1 and MUC2 negative and MUC5A positive. There are significant histopathological similarities between low-grade, branch-type IPMN and some PanIN, particularly PanIN 1A and 1B lesions [1, 6, 10, 11, 13, 21, 24]. The pure GF-IPMN very rarely involve the main pancreatic duct and very rarely progress to invasive carcinoma. Some IPMN present more than one direction of differentiation. I-IPMN and PB-IPMN may have a GF component [11, 21].

To our knowledge, no study regarding the directions of differentiation of IPMN diagnosed in Polish centres has been published.

We present a histopathological and immunohistochemical study of pure GF-IPMN, which arose in the distal portion of the main pancreatic duct and progressed to invasive tubular carcinoma. Additionally, many intraductal lesions resembling IPMN with low-grade dysplasia or PanIN 1A/1B lesions within interlobular and intralobular pancreatic ducts as well as invasion of the ampulla of Vater and duodenal wall were observed.

Case report

A 69-year old man reported abdominal pain, anorexia and weight loss (12 kg) for a period of 8 weeks and obstructive jaundice with pruritus for 4 weeks. Abdominal CT revealed an enlarged gallbladder and a 4 cm pancreatic mass. No infiltration or encasement of the celiac trunk and mesenteric arteries and no distant metastases were found. Magnetic resonance cholangiopancreatography revealed a neoplastic cyst (diameter 2 cm) in the pancreatic head, and dilated intra- and extrahepatic biliary tract (common hepatic duct and common bile duct up to 2 cm in their maximum diameter) and main pancreatic duct. Endoscopy revealed a reddened and fibrin-covered orifice of the ampulla of Vater. In endoscopic biopsy of the ampulla of Vater chronic inflammation was noted. The patient was submitted to surgery, and a pylorus-preserving pancreaticoduodenectomy was performed. No frozen sections or cytological examinations were done. In the postoperative period the patient developed ascites, bilateral hydrothorax, persistent cholestasis, and delayed gastric emptying. After successful conservative treatment the patient was discharged from the hospital on the 30th postoperative day. Unfortunately, he was lost to follow-up.

The pancreaticoduodenectomy specimen was fixed in buffered formalin. Gross examination was done according to the recommendations of Luttges, Zamboni and Kloppel (with some modifications, because a fresh specimen was not available for examination) [27] and the College of American Pathologists (CAP) [28]. Unfortunately, due to the retrospective nature of the study, the status of recently described margins (anterior radial and medial) [1, 29] could not be assessed. Tissue blocks were routinely embedded in paraffin, processed and sectioned. Tissue sections were stained with hematoxylin and eosin.

Histopathological diagnosis of IPMN was based on AFIP [1] and World Health Organization (WHO) [9] definitions and recommendations. Differentiation of the intraductal component was assessed based on an international consensus study [6]. Histopathological grading of invasive carcinoma was based on the scheme proposed by Kloppel et al. [12, 30] and a new scheme proposed by Adsay et al. [31]. The growth pattern of IPMN was described according to recent definitions proposed by Nara et al. [32]. Staging was assessed based on the American Joint Committee on Cancer (AJCC) Staging Atlas [33].

Histochemical mucicarmine stain for mucins was made in the standard manner [34]. Additionally, immunohistochemical stainings were performed (Table I). The technique was similar to our previous IPMN report [35]. All immunohistochemical assays were carried out on paraffin-embedded tissue, using an automated staining machine (Autostainer Plus, Dako, Glostrup, Denmark) after heat-induced antigen retrieval. EnVision-HRP (Dako, Glostrup, Denmark) kit with diaminobenzidine and counterstaining with hematoxylin was used for visualization. In the negative control, the primary antibodies were substituted with antibody diluent (buffer and bovine serum albumin carrier protein, Roche Diagnostics, Mannheim, Germany).

p53 and cyclin D1 nuclear stainings were considered positive. Loss of p16^{INK4A} expression was noted when no nuclear staining in neoplastic cells was observed,

Table I. Primary antibodies
Tabela I. *Przeciwciała pierwotne*

Antibody	Clone	Positive control
p53	DO-7	ductal adenocarcinoma of the pancreas
Cyclin D1	P2d11f11	nodal mantle cell lymphoma
$P16^{INK4A}$	JC8	islet cells, stromal cells
CEA	IL-7	colon
Chromogranin	Polyclonal	islet cells
Synaptophysin	Polyclonal	islet cells
Ki-67	MIB1	ductal adenocarcinoma of the pancreas

whereas positive nuclear staining in islet cells and stromal cells was observed [36]. CEA immunohistochemical membranous and cytoplasmic staining was considered positive. Cytoplasmic chromogranin and synaptophysin staining was considered positive. The proliferative Ki-67 index was presented as the percentage of positive cells among 200 counted cells (separately in the intraductal and invasive component).

The study was performed in conformity with the guidelines of the Helsinki Declaration.

A surgical specimen including duodenum measuring 13 cm with pancreatic head (5 × 4.5 × 4 cm) and gallbladder was submitted for gross examination. In the pancreatic head a white, irregular, solid mass localized within the pancreatic head around the main pancreatic duct was observed. The diameter of the pancreatic duct was 2 cm with visible papillary projections into the lumen of the duct. Grossly, no signs of obvious invasion of the duodenal wall and ampulla of Vater were seen. The pancreatic tissue was firm and suggestive of chronic pancreatitis. The common bile duct seemed not to be involved by the tumour, although it was dilated up to 2.5 cm in diameter in the proximal portion. Group I lymph nodes (anterior and posterior pancreaticoduodenal nodes) [27] were dissected and submitted entirely for histopathological examination.

On microscopic examination the lesion within the distal portion of the main pancreatic duct was an intraductal neoplasm. It was composed of well-developed, thick, long papillae, formed of fibrovascular cores lined with mucin-secreting columnar cells (Figs 4A, 4B). The cytoplasm of neoplastic cells was slightly eosinophilic, and contained abundant cytoplasmic, supranuclear mucin. The nuclei were basally oriented and moderate cytological atypia was seen. No areas composed of intestinal-type or pancreatobiliary-type papillae were seen. Acellular mucin pools and ovarian-like stroma beneath the intraductal component were absent.

The invasive component of the neoplasm was composed of small, well-formed tubules and infiltrating neoplastic cells (Fig. 4C). The entire tumour was an infiltrating ductal adenocarcinoma (according to recent AFIP nomenclature, tubular adenocarcinoma). The well-formed tubules resembled the benign-appearing variant of pancreatic ductal adenocarcinoma known as foamy cell carcinoma [37], although this variant of pancreatic carcinoma is derived from PanIN (not IPMN) and individual infiltrating cells are not typical for it. Infiltrating neoplastic cells were dispersed among the tubules. The amount of mucin production, mitotic count and nuclear features in these cells were virtually the same as in the well-differentiated component. No colloid differentiation was observed.

There was abundant intracellular mucin within the invasive component and moderate pleomorphism of neoplastic cells. The mitotic count was 4 per 10 high-power-fields. The sum of Kloppel's grading scores was 7 [moderate nuclear pleomorphism – 2, mitotic index less than 5 mitoses per 10 high-power fields – 1, intensive mucin production – 1, poor glandular differentiation ("higher grade" of tumour was taken into account) – 3]. Overall grading index was 1.75 (7/4) and the tumour grade according to Kloppel's scheme [12, 30] was 2 (G2). The tumour grading score according to the scheme proposed by Adsay et al. [31] was 4 (1+3) – well-formed tubular units were assessed as pattern 1, individual cell infiltration was assessed as pattern 3. Moderate level of differentiation was diagnosed.

The growth pattern was infiltrative according to the definition proposed by Nara et al. [32]. The distance from the deepest point of invasion to the stromal surface of the nearest non-invasive carcinoma (the largest diameter of the largest invasive focus, the size of the tumour) was 2.1 cm; therefore the tumour extended beyond the border (0.5 cm) of minimal invasion.

On microscopic assessment, the duodenal wall and ampulla of Vater were infiltrated by the neoplasm,

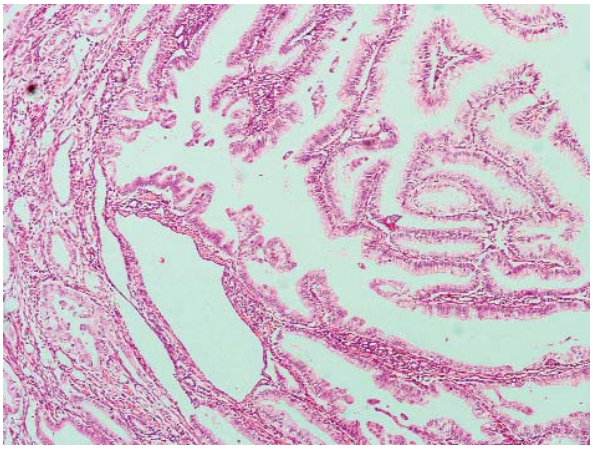

Fig. 4A. Intraductal papillary mucinous neoplasm of the pancreas (gastric foveolar type). Intraductal component. Magn. 100×
Ryc. 4A. *Wewnątrzprzewodowy brodawkowaty nowotwór śluzowy trzustki (wariant żołądkowo-dołeczkowy). Utkanie wewnątrzprzewodowe. Powiększenie 100×*

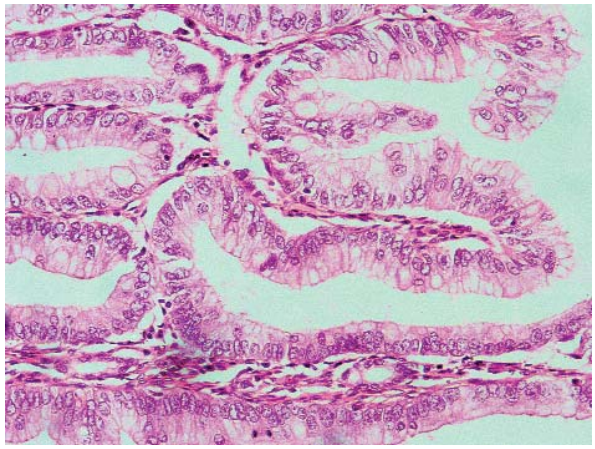

Fig. 4B. Intraductal papillary mucinous neoplasm of the pancreas (gastric foveolar type). Intraductal component. Magn. 400×
Ryc. 4B. *Wewnątrzprzewodowy brodawkowaty nowotwór śluzowy trzustki (wariant żołądkowo-dołeczkowy). Utkanie wewnątrzprzewodowe. Powiększenie 400×*

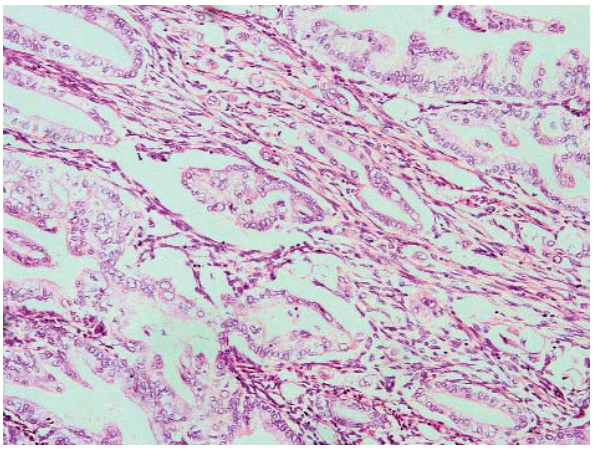

Fig. 4C. Tubular (ductal) carcinoma G2 derived from intraductal papillary mucinous neoplasm of the pancreas. Magn. 200×
Ryc. 4C. *Rak cewkowy (przewodowy) o średnim stopniu zróżnicowania wywodzący się z wewnątrzprzewodowego brodawkowatego nowotworu śluzowego trzustki. Powiększenie 200×*

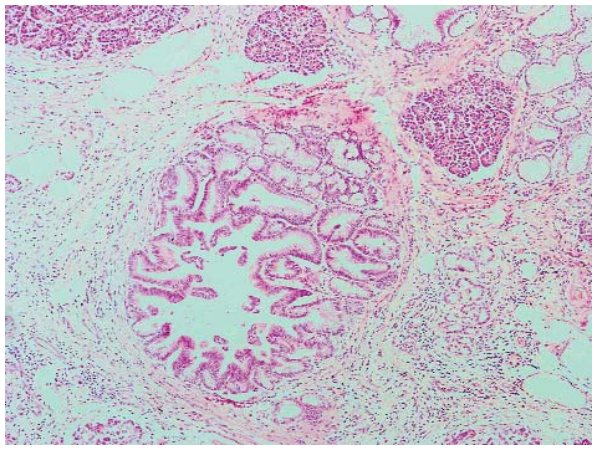

Fig. 4D. The distal portion of intraductal papillary mucinous neoplasm of the pancreas, resembling pancreatic intraepithelial neoplasia. Magn. 40×
Ryc. 4D. *Dystalna cześć wewnątrzprzewodowego brodawkowatego nowotworu śluzowego trzustki przypominająca nowotworzenie wewnątrznabłonkowe (neoplazję śródnabłonkową). Powiększenie 40×*

although the invasion was rather subtle, without destruction of these structures. No venous or perineural invasion was observed, although lymphatic invasion was seen. Lymph node metastases were not observed.

In the pancreatic tissue within the pancreatic head outside the main lesion, many intraductal lesions in the intralobular and interlobular branches, composed of mucinous cells forming micropapillary projections (GF-IPMN with low-grade dysplasia, or low-grade PanIN-like complexes), were observed (Fig. 4D) [5]. These lesions were not seen macroscopically. If there was no tumour in the specimen, these lesions would

probably be diagnosed as PanIN 1A and PanIN 1B lesions. Considering the distribution of low-grade PanIN-like complexes and location of the IPMN, and based on the results of the study of Biankin et al. [36], these lesions were believed to represent the distal portion of the intraductal component of the IPMN. Adopting the nomenclature used for describing breast lesions [38], the extent of the disease (area of invasive and non-invasive component) was assessed as 4.1 cm, and size of the tumour, as described previously, was 2.1 cm.

There are no clear definitions of main duct type, branch duct type and mixed type of IPMN [1]. Particularly, distinguishing main duct type IPMN from mixed type IPMN is ambiguous. In the presented case the main portion of the non-invasive component was present within the main pancreatic duct, so the diagnosis of main duct type IPMN was made.

Resection margins (proximal and distal duodenal margin, common bile duct margin, pancreatic transection margin, posterior radial margin) were free of tumour. Unfortunately, the anterior radial margin and medial margin [1, 29] could not be assessed. At the time when the gross examination was done (before the concept of anterior and medial margins was introduced in reference sources) the extent of resection was assessed as R0 (complete resection without residual macroscopic or microscopic tumour) [1]. No PanIN/IPMN lesions in the pancreatic transection margin were observed.

The final diagnosis, according to AFIP nomenclature [1], was: pure gastric-foveolar variant of intraductal papillary mucinous neoplasm of the pancreas (main duct type) with an associated moderately differentiated (G2) invasive tubular carcinoma. According to WHO [9] and CAP [28] nomenclature, invasive papillary-mucinous carcinoma was diagnosed. AJCC stage was pT3N0M0V0L1 (stage IIa) [1, 26, 28].

In differential diagnosis several lesions were taken into account: invasive carcinoma derived from PanIN within the main pancreatic duct, mucinous cystic neoplasm (MCN) with an associated invasive carcinoma, pancreaticobiliary metaplastic variant of ampullary papillary adenocarcinoma, GF-IPMN of the common bile duct, and coexistence of IPMN with invasive tubular carcinoma not derived from it.

PanIN are usually small (less than 1 cm) lesions within the intralobular and interlobular branches (although infrequently they may be observed in the main pancreatic duct) and rarely if ever form complex, thick or long papillae.

About 99% of MCN arise in women, particularly in the pancreatic tail. MCN do not usually communicate with the pancreatic duct. According to the AFIP definition [1], in MCN ovarian-type stroma is always present.

A pancreaticobiliary metaplastic variant of ampullary papillary adenocarcinoma has been described [39]. It is composed of mucinous epithelium "with differentiation of gastric-type metaplasia" and is characterized by intense MUC5AC staining, faintly positive MUC1 staining and negative MUC2 staining [39]. The precise assessment of localization of a small ampullary tumour (this indicates whether the tumour originates from the ampulloduodenum, the ampullopancreaticobiliary common duct, the ampullopancreatic duct, or ampullobiliary duct) [39, 40] is, in our opinion, possible only if the fresh, unfixed pancreaticoduodenectomy specimen is bisected along the plane created by the common bile duct and main pancreatic duct with a sharp knife after probing the ducts separately. Probing the ducts in a fixed specimen is probably impossible or it may lead to destruction of the ducts (risk of creating false canals). Therefore, we were not able to describe precisely the relationship between the tumour and the ampullopancreatic duct. Sections taken in the horizontal plane showed that invasion of the ampulla of Vater and duodenal wall was present, but a well-defined neoplastic mass within these structures was absent. The main bulk of the tumour was localized within the pancreatic head – extensive infiltration of the pancreatic head by ampullary carcinoma without total destruction or extensive infiltration of the whole ampulla and adjacent duodenal wall is, in our experience, doubtful. The extent of the tumour (particularly of the non-invasive component within small pancreatic ducts) also indicates that the neoplasm arose within the pancreatic duct and not in the ampulla of Vater.

GF-IPMN of the common bile duct was excluded, since gross and microscopic examination of the common bile duct revealed no tumour.

Coexistence of two neoplasms (collision tumour) was also excluded. The main portion of the intraductal component of the neoplasm was surrounded by infiltrating adenocarcinoma. An area with destruction of the pancreatic duct wall by intraductal neoplasm and progression to infiltrating adenocarcinoma was also seen. No PanIN 2 or PanIN 3 lesions, which are usually noted in pancreatic tissue next to the ductal adenocarcinoma (including the foamy gland variant), were seen.

Additionally, chronic pancreatitis and chronic cholecystitis were noted.

Histochemical mucicarmine stain revealed a large amount of intracellular mucin in the intraductal and

invasive component. Scattered chromogranin-positive and synaptophysin-positive endocrine cells in the intraductal and invasive component were noted. The apical portion of neoplastic cells in the intraductal and invasive component was labelled with anti-CEA antibody (Figs 4E, 4F). About 5% of cells in the intraductal and invasive component were cyclin D1-positive. The proliferative Ki-67 index was 15 and 10% in the invasive and intraductal component, respectively (Figs 4G, 4H). No expression of p53 or $p16^{INK4A}$ was observed.

Discussion

Gastric-foveolar differentiation is present in 31-51% of IPMN, but pure GF-IPMN associated with invasive carcinoma make up less than 2% of all IPMN [5, 13, 20, 21].

The mean age of patients with GF-IPMN is 66 years and is comparable to the age of patients with I-IPMN and PB-IPMN [5, 20]. Men are affected about 1.6-5 times more often than women [5, 20], but higher incidence of all IPMN types among men is typical [20]. The long-term prognosis in patients with I-IPMN is probably worse than in patients with GF-IPMN (5-year survival rates 62 and 100%, respectively) [20], but other authors state that survival in patients with GF-IPMN and I-IPMN is very similar [21].

GF-IPMN are smaller (mean diameter 2.6 cm) than I-IPMN and PB-IPMN (mean diameter: 5.5 and 4 cm, respectively) [21]. From 48 to 80% of GF-IPMN are characterized by low-grade dysplasia, and this is more frequent than for I-IPMN (from 0 to 14%) [5, 13, 20, 21, 41]. Invasive carcinoma is present in less than 7% of patients with GF-IPMN [5, 13, 20], but in two studies invasive carcinoma was present in 17 and 27% of patients with GF-IPMN [10, 21]. Invasive carcinomas derived from GF-IPMN typically have a tubular pattern [5, 13, 20, 21]. No case of invasive colloid carcinoma (which is typical for I-IPMN) derived from pure GF-IPMN has been described. From 80 to 98% of GF-IPMN arise in branch pancreatic ducts, and this is more frequent than for I-IPMN (27-37%) [5, 13, 15, 20]. Low-grade PanIN-like intraductal lesions are present in 80% of patients with GF-IPMN and in 3% of patients with I-IPMN [5]. Complete atrophy of pancreatic parenchyma near GF-IPMN is almost never seen, but it may be present in up to 60% of patients with I-IPMN [5]. Intraluminal nodular growth is typical for intestinal type IPMN and in GF-IPMN it is rarely observed [5].

p53 overexpression (defined as nuclear staining in at least 10 or 25% of cells), cyclin D1 overexpression (defined as nuclear staining in at least 5% of cells) and loss of $p16^{INK4A}$ expression (defined as described earlier) is seen in about 80% of invasive carcinomas derived from IPMN [18, 36, 42]. In some studies no differences in p53 expression between non-invasive and invasive component were observed [22]. Similarly to PanIN, p53 accumulation is more frequent in high-grade IPMN than in low-grade IPMN [22], although p53 overexpression is less frequent in IPMN than in PanIN

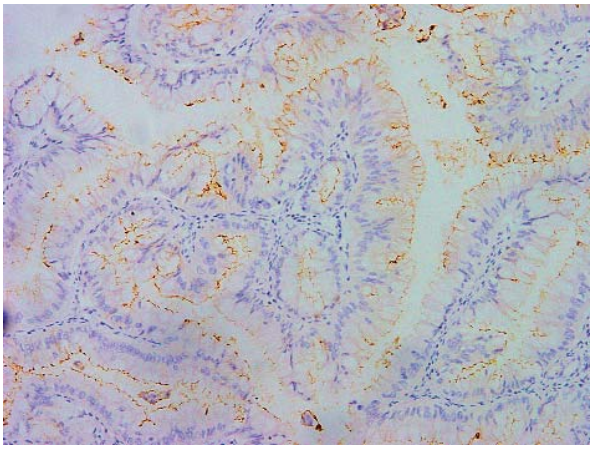

Fig. 4E. CEA immunostaining. Intraductal component. Magn. 200×
Ryc. 4E. *Barwienie immunohistochemiczne CEA. Utkanie wewnątrzprzewodowe. Powiększenie 200×*

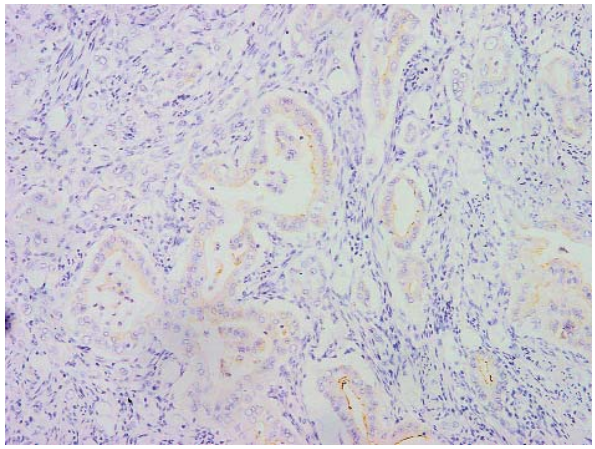

Fig. 4F. CEA immunostaining. Invasive component. Magn. 200×
Ryc. 4F. *Barwienie immunohistochemiczne CEA. Utkanie inwazyjne. Powiększenie 200×*

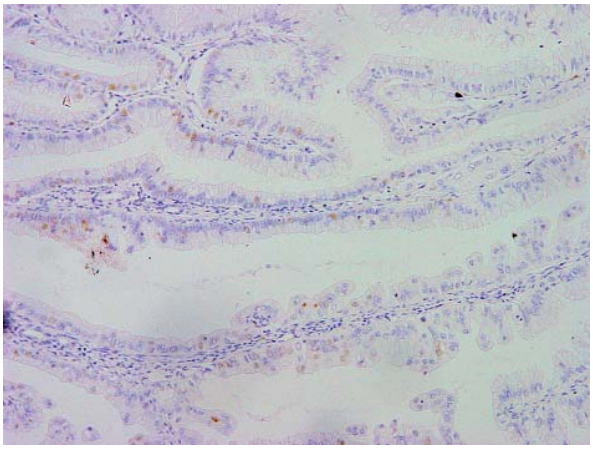

Fig. 4G. Ki-67 immunostaining. Intraductal component. Magn. 200×
Ryc. 4G. *Barwienie immunohistochemiczne Ki-67. Utkanie wewnątrzprzewodowe. Powiększenie 200×*

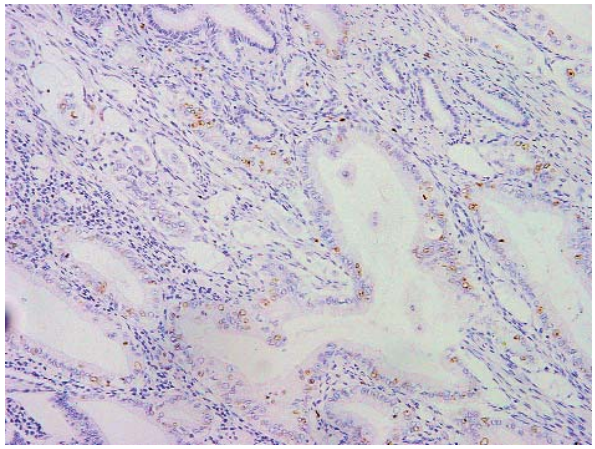

Fig. 4H. Ki-67 immunostaining. Invasive component. Magn. 200×
Ryc. 4H. *Barwienie immunohistochemiczne Ki-67. Utkanie inwazyjne. Powiększenie 200×*

[18, 21]. During pancreatic carcinogenesis, overexpression of p53 and cyclin D1 typically appears between stages of PanIN 2 and PanIN 3 lesion [18, 21, 36]. The percentage of p53-positive non-invasive IPMN varies from 0 to 50% [1]. The negative result of p53 immunohistochemical staining in the presented case (both in the intraductal as well as in the invasive component) indicates that alteration of the *TP53* gene is not necessary for progression of intraductal carcinoma to invasive carcinoma.

Cyclin D1 overexpression is more common in IPMN with high-grade dysplasia than in lower-grade lesions [42]. It is observed in the majority, but not in all cases of invasive carcinoma derived from IPMN. As noted earlier, in the presented case cyclin D1 expression was observed in about 5% of cells in the intraductal and in the invasive component.

Data referring to the percentage of loss of $p16^{INK4A}$ expression within IPMN are discrepant [1, 18]. According to some authors, the percentage of loss of $p16^{INK4A}$ expression is lower in patients with low-grade IPMN in comparison with patients with high-grade IPMN [42], similarly to low-grade and high-grade PanIN [36]. In the course of pancreatic carcinogenesis, loss of $p16^{INK4A}$ expression typically presents at the stage of PanIN 1B or PanIN 2 lesion [18, 21, 36]. It should be clearly stated that loss of $p16^{INK4A}$ expression in the presented case indicated genetic alteration of the *CDKN2A/INK4A* gene resulting in lack of immunohistochemical staining.

The CEA immunostaining in IPMN usually, but not always, changes according to grades of dysplasia from purely apical through cytoplasmic to diffuse [32]. Some conflicting reports regarding the CEA immunohistochemical staining polarity in IPMN have been published [22, 32]. Apical CEA staining in the invasive component, as in the presented case, indicates that at least some aspects of mechanisms involved in maintaining the polarity of the cell were still present.

Scattered chromogranin-positive and synaptophysin-positive cells are observed in IPMN [32, 43], as in the presented case. The origin of these cells and their influence on IPMN biology is not clearly determined [43].

The proliferative Ki-67 index in IPMN with low-grade, moderate-grade and high-grade of dysplasia and in invasive carcinoma derived from IPMN is 4.6, 16.9, 39.8 and 47.4%, respectively [32]. Increase of proliferative Ki-67 index during grading of cytoarchitectural dysplasia in IPMN is clearly seen [32]. In the presented case, a difference in the proliferative Ki-67 index between the intraductal and invasive component was noted.

There are many controversies regarding GF-IPMN status [5, 21]. The prevalence of GF-IPMN in distal portions (in branch ducts away from the main lesion) of other types of IPMN has not been clearly determined, but it may be high.

Initially, it was believed that I-IPMN and PB-IPMN represent different grades of dysplasia, but at present it is clear that these are distinct types of IPMN, which not only have different histological patterns but also represent different pathways of carcinogenesis and probably are of different clinical significance [11, 21].

The role of GF-IPMN in these pathways is not clear. It may be a precursor lesion for IPMN with a higher degree of dysplasia [5, 11, 21, 24], which (along with lack of MUC1 and MUC2 expression) explains the potential progression of GF-IPMN towards I-IPMN and PB-IPMN. Low-grade GF-IPMN may progress to both I-IPMN and PB-IPMN with moderate or high-grade dysplasia [11, 21, 24]. Transformation from I-IPMN to PB-IPMN is probably possible [11].

Another hypothesis states that there are different pathogenetic mechanisms regarding progression of GF-IPMN and I-IPMN, and coexistence of moderate or high-grade I-IPMN with a low-grade GF-IPMN component results from the fact of the I-IPMN overgrowth over GF-IPMN [5].

GF-IPMN shows 4, 8 and 4% expression of MUC1, MUC2 and CDX2, respectively [21]. MUC2 expression is present in scattered goblet cells in GF-IPMN [5]. A marker of GF differentiation, MUC5AC, is expressed in virtually all GF-IPMN, in all I-IPMN, in PanIN, in MCN and in ductal adenocarcinoma, but not in normal ductal epithelium. This fact indicates that GF differentiation is widespread in pancreatic lesions, particularly in precursors for pancreatic adenocarcinoma [5, 6, 18, 25].

The molecular and histopathological similarity of small low-grade GF-IPMN and low-grade PanIN indicates that there may be some similarities or even common features in the pathogenesis of both these lesions. Coexistence of PanIN-like structures with GF-IPMN may indirectly support this hypothesis [5, 10, 15]. Additionally, small early IPMN may not be distinguishable from PanINs [10, 11, 24, 36]. Additionally, a similar MUC profile in GF-IPMN and PanIN (MUC5AC-positive, MUC1-negative and MUC2-negative) is observed [10]. It was recently speculated that GF-IPMN may be a large PanIN lesion [10]. However, such large papillary projections as in the presented case are never seen in a PanIN lesion.

A GF variant of papillary cholangiocarcinoma (intraductal papillary mucinous neoplasm of the bile duct) has been described, although biliary GF-IPMN are less frequent than pancreatic GF-IPMN [41, 44, 45]. Biliary GF-IPMN share an immunohistochemical profile with pancreatic GF-IPMN [44], which indirectly indicates the common pathogenic mechanisms involved in the development and progression of IPMN.

A pancreaticobiliary metaplastic variant of ampullary papillary adenocarcinoma "with differentiation of gastric-type metaplasia" has been described [39]. The immunohistochemical and genetic characteristics of intestinal-type and pancreaticobiliary-type ampullary carcinomas is well described, and some features of these tumours resemble parallel types of pancreatic and biliary tumours [39, 40, 46, 47].

The described case of gastric-foveolar variant of intraductal papillary mucinous neoplasm of the pancreas without intestinal or pancreaticobiliary differentiation indicates that future studies concerning pancreatic carcinogenesis and particularly cancer precursor lesions are needed. The dichotomous model of IPMN progression (intestinal pathway or pancreaticobiliary pathway) is obviously very simple and it is possible that not all cases of IPMN develop clearly in these two ways.

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