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CASE REPORT

Collision of a neuroendocrine tumor and ductal adenocarcinoma of the pancreas: a rare case report

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Abstract

Despite the increased incidence of pancreatic cancer, reported data of collision pancreatic tumors are very rare, limited just to sporadic cases. There are only two described cases of the collision pancreatic tumor consisting of neuroendocrine and pancreatic ductal adenocarcinoma in the literature. Currently, we are presenting a case of a young female patient with pancreatic ductal adenocarcinoma surrounding a smaller focal lesion of the well-differentiated neuroendocrine pancreatic tumor. The patient underwent proximal pancreaticoduodenectomy with uneventful postoperative course. Histogenesis of these colliding tumors remains unclear. However, there are several proposed theories. Surgical resection could be the treatment of choice of resectable cases; however, preoperative diagnosis is virtually impossible.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) ranks the fourth on the list of cancer-related causes of death and surgical resection is currently the only chance for a cure, improving five-year survival rates from <4% if left untreated to 25–30% after resection (Jemal *et al.* 2009). Three different types of precursor lesions of PDAC have been identified: pancreatic intraepithelial neoplasia (PanIN), mucinous cystic neoplasia (MCN), and intraductal pancreatic mucinous neoplasia (IPMN) (Ottenhof *et al.* 2011).

However, collision tumors of the pancreas are very rare and reported data are limited only to sporadic cases. There is a clear difference between mixed and collision tumors, the former group contains closely mixed non separated cells while in the latter tumor cells are strictly separated. Collision tumors of the pancreas are most frequently matter of incidental and surprising findings in the histopathologic specimen after surgical resection. Histogenesis of these colliding tumors remains unclear. However, there are several proposed theories.

CASE REPORT

A 45-year-old female patient was investigated for recurrent attacks of acute pancreatitis with weight loss of 16 kg, associated with the new onset of diabetes requiring insulinotherapy. During the last

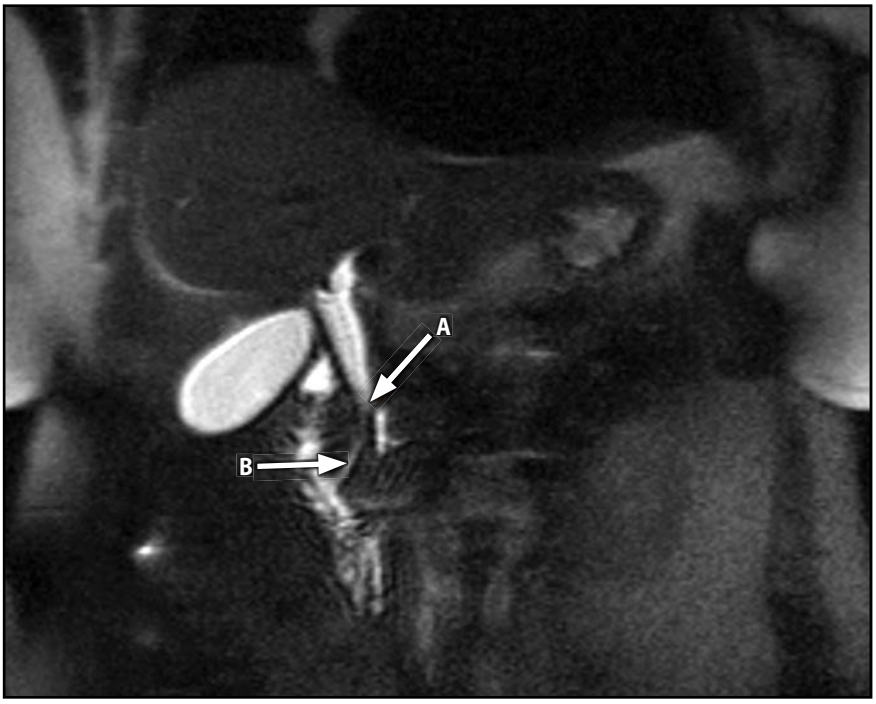

Fig. 1. MRCP finding: A – conic narrowing of the common bile duct. B – stenotic retropancreatic portion of the common bile duct (length of 30 mm)

attack of pancreatitis, obstructive jaundice developed and ERCP with implantation of the duodenobiliary stent was performed. Subsequently, jaundice resolved. Biliary obstruction resulted from the terminal stenosis of the common bile duct in length of 3 cm, there was dilatation of the intrahepatic biliary tree and pancreatic duct was well. The histologic examination of endoscopic biopsy showed signs of high-grade dysplasia with high suspicion of adenocarcinoma of the pancreatobiliary type.

Preoperative MRCP and CT

MRCP revealed dilatation of the extrahepatic bile ducts, bilateral dilatation of intrahepatic bile ducts and dilatation of the main pancreatic duct (Fig. 1). The head of the pancreas was inhomogeneous without invasion to adjacent structures. There were no signs of regional lymphadenopathy and no signs of distant metastases. The CT finding was more valuable showing a hypodense tumor of the pancreatic head and uncinate process measuring 35x25x30mm with the

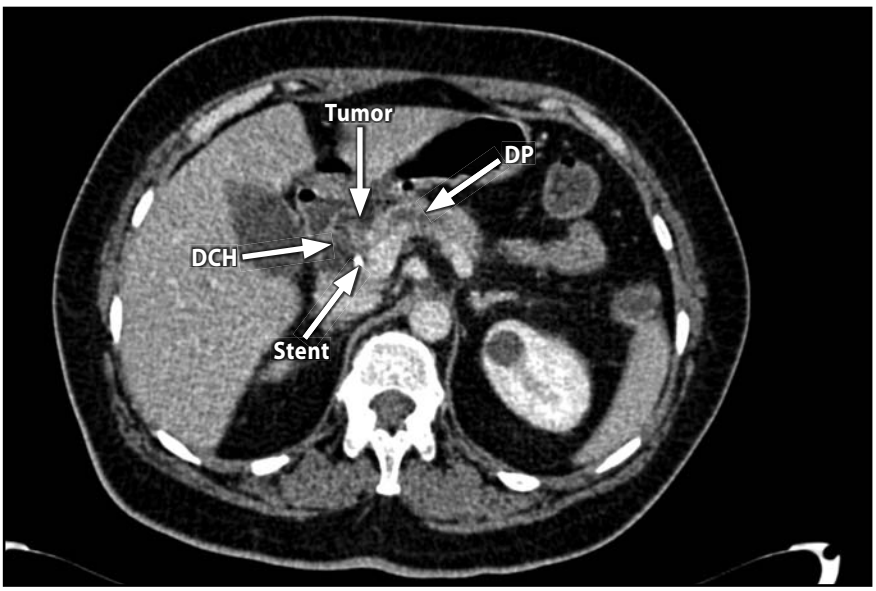

Fig. 2. CT scan: DP – ductus pancreaticus (pancreatic duct). DCH – ductus choledochus (common bile duct)

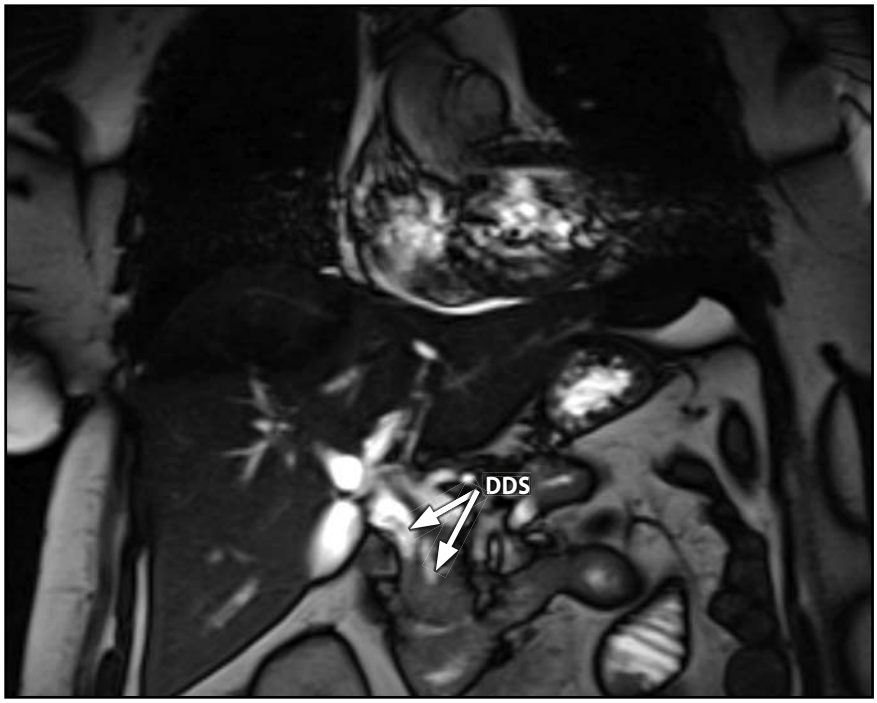

Fig. 3. Double-duct sign (arrows)

resulting double-duct sign (Fig. 2, 3). CT confirmed intra and extrahepatic bile duct dilatation (the size of the dilated common bile duct was 15mm) with presence of biliary stent inside. There were no CT signs of acute pancreatitis, no fluid collections. One enlarged retropancreatic lymph node sized 11mm, as well as multiple infrarenal retroperitoneal aortocaval lymph nodes, were revealed. Preoperative laboratory parameters on admission are listed in Table 1. Preoperative serum tumor marker levels are listed in Table 2. There was a past medical history of NIDDM, liver steatosis, hyperlipoproteinemia and chronic tobacco abuse. Twelve hours before elective procedure the signs of acute cholangitis with mild epigastric tenderness and jaundice appeared with serum bilirubin level elevation to 108.6 mmol/l. The patient was sub-

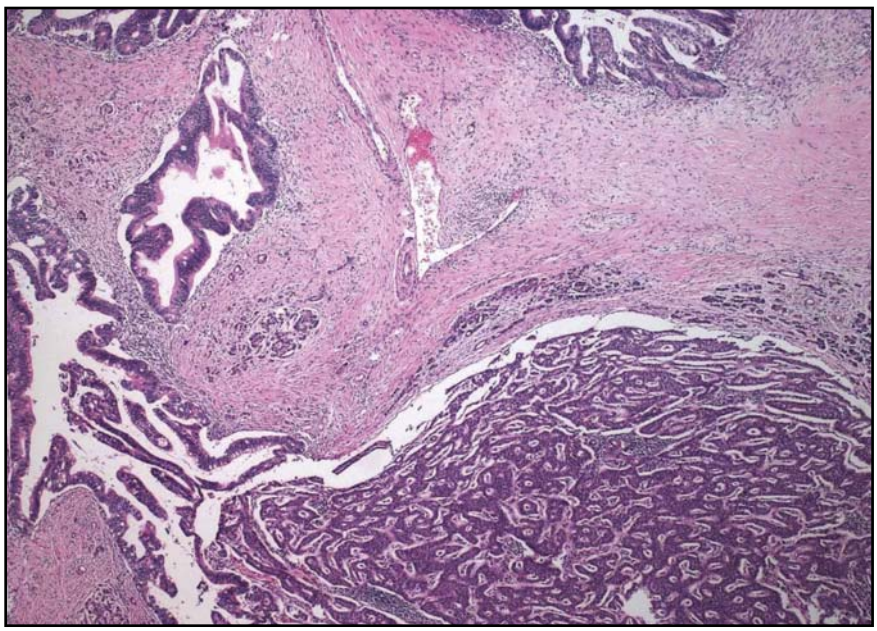

Fig. 4. Collision tumors: well differentiated neuroendocrine tumor in the lower part and infiltrating glands of ductal carcinoma in the upper part of the picture; the close margin between both tumors is clearly visible (H&E; 40x)

Tab. 1. Preoperative laboratory parameters on admission

Laboratory parameter	Value	Reference interval
WBC [G/l]	8.00	4.00 - 10.00
RBC [T/l]	4.44	3.90 - 5.20
HGB [g/l]	129	125 - 165
PLT [G/l]	270	150 - 420
LYMPHOCYTES [%]	36.7	18 - 44
MONOCYTES [%]	6.6	3 - 10
NLR	1.48	<2.30
PLR	93.10	<300
QUICK [%]	94	75 - 130
APTT [sec]	27.5	23 - 35
FIBRINOGEN [g/l]	4.54	1.8 - 3.5
ATIII [%]	115.0	75 - 125
D-DIMER [mg/l]	0.25	0.00 - 0.30
GLUCOSE [mmol/l]	11.04	3.90 - 5.50
ALBUMIN [g/l]	40.9	35.0 - 52.0
TOTAL BILIRUBIN [µmol/l]	8.6	3.4 - 17.1
AST [µkat/l]	0.77	0.60
ALT [µkat/l]	0.96	<0.60
GMT [µkat/l]	4.74	<0.63
ALP [µkat/l]	3.53	0.70 - 1.63
CRP [mg/l]	10.3	<5.0

Tab. 2. Preoperative serum tumor marker levels

Laboratory parameter	Value	Reference interval
CEA [ng/ml]	1.2	<4.0
CA 19-9 [IU/ml]	139.5	<35.0
TPS [IU/l]	44	<80
NSE [ng/ml]	9.3	<12.5
CHROMOGRANIN A [ng/ml]	225.9	<101.9

Tab. 3. Dynamics of biochemical parameters during 12 hours

Laboratory parameter	Value	Reference interval
TOTAL BILIRUBIN [µmol/l]	108.6	3.4 - 17.1
GMT [µkat/l]	10.03	<0.63
AMYLASE [µkat/l]	0.76	<1.67
LIPASE [µkat/l]	1.03	<1.12
CRP [mg/l]	142.4	<5.0
WBC [G/l]	15.50	4.00 - 10.00
LYMPHOCYTES [%]	4	18 - 44
MONOCYTES [%]	4.6	3 - 10
NLR	23.50	<2.30
PLR	350.00	<300.00

febrile 37.5 °C with concomitant inflammatory markers elevation: GMT raised to 10.03, leukocyte count increased from 8.00 to 15.50, CRP 142.4 from 10.3 and NLR reached 23.50 (Table 3).

Because of the very short duration of abovementioned symptoms, the patient was admitted for the elective surgical procedure. Proximal pancreaticoduodenectomy with Child-Stulhofer reconstruction was performed at the Department of Surgical Oncology of St. Elisabeth Cancer Institute. Intraoperatively we did not find any signs of dissemination. We revealed dislocation of biliary stent that might be responsible for cholangitis and presence of roily bile in the dilated bile duct. The superior mesenteric vein (SMV) was encapsulated by desmoplastic tissue but without its invasion. SMV was successfully separated from pancreatic tissue without need for vascular resection. Operation time was 360 min, blood loss of 300ml with no need for blood transfusion. The postoperative course was uneventful; the patient was discharged on the 10th POD.

Macroscopically, the resected specimen composed of the stomach, duodenum, common bile duct, jejunum and pancreas with a total length of 27 cm was sent to the department of pathology for investigation. In the pancreas, there was found a firm white tumor located in the head which directly extended to the uncinate process and grossly incorporated the common bile duct. The tumor was 25 x 40 mm in size and on the cut surface it had a heterogeneous structure.

The microscopic examination of the pancreatic tumor showed typical glands of moderately differentiated ductal carcinoma in the majority of the tumor fields, moreover, in one section there was also detected a small focus of well differentiated neuroendocrine tumor (NET), sized 6 x 13 mm and located inside pancreatic parenchyma, without signs of invasion into peripancreatic tissues. Both tumors were in very close relation, without clear intermingling (Fig. 4, 5).

Prevailing ductal carcinoma was composed of infiltrative tubular, larger glandular and cribriform structures with focal micropapillary pattern embedded in voluminous desmoplastic and sclerotic stroma, areas of perineural and intravascular propagation, small coagulation necrosis and hemorrhages were also disclosed. Ductal carcinoma directly infiltrated into peripancreatic lipomatous tissue, the wall of the duodenum and common bile duct and spread into regional lymph nodes. Nine out of eighteen lymph nodes were positive (Fig. 6). Well differentiated NET exhibited trabecular architecture, neoplastic cells were small, without marked atypia. The mitotic and prolif-

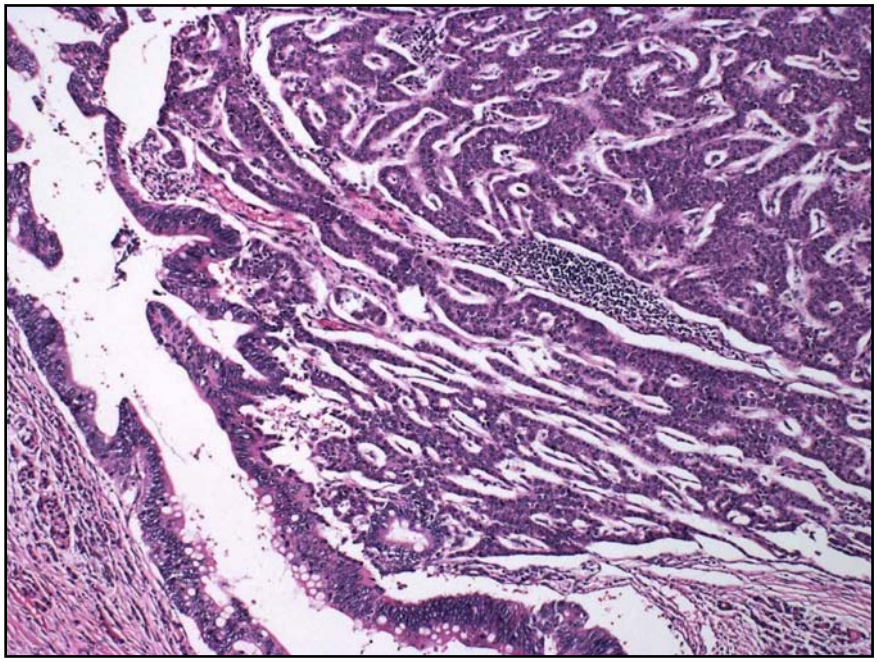

Fig. 5. Detail on trabecular structures of the well differentiated neuroendocrine tumor with small neoplastic cells without atypia (right) and malignant gland of the ductal carcinoma with pseudostratification and a high degree of cellular atypia (left) (H&E; 200x)

erative activity (measured by Ki-67) were very low and tumor was classified as grade 1.

Immunohistochemistry revealed positivity of chromogranin A (Fig. 7), synaptophysin and glucagon in the cells of NET, whereas structures of ductal carcinoma were negative. Ductal carcinoma showed positive staining of cytokeratin 7 (Fig. 8), cytokeratin 20 and CDX-2, these were absent in the cells of NET. Both tumors had positivity for cytokeratin 18. Ki-67 was below 1% of positive cells in the area of NET and about 60% of positive cells in the part of ductal carcinoma (Fig. 9).

Immunohistochemistry: pancreatic ductal adenocarcinoma: CK7+, CK20 +, CK18+, PAX8-, CDX-2-, Ki-67: cca 60% posit., neuroendocrine tumor: CK18+, chromogranin A+, synaptophysin+, PAX8-, CDX-2-, glucagon+, insulin-, somatostatin-, gastrin-, Ki-67 1%.

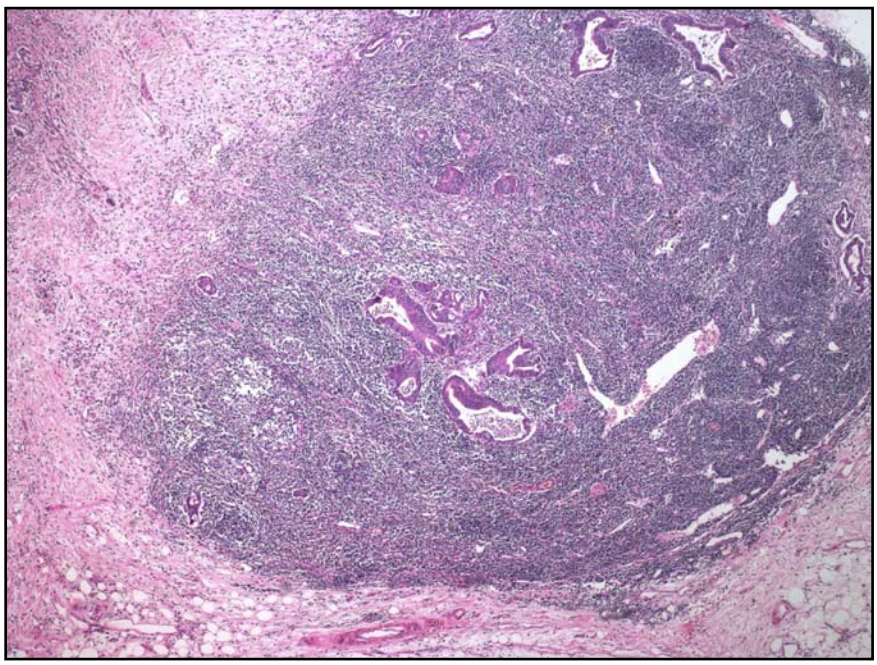

Fig. 6. Metastasis of ductal carcinoma in the regional lymph node (H&E; 40x)

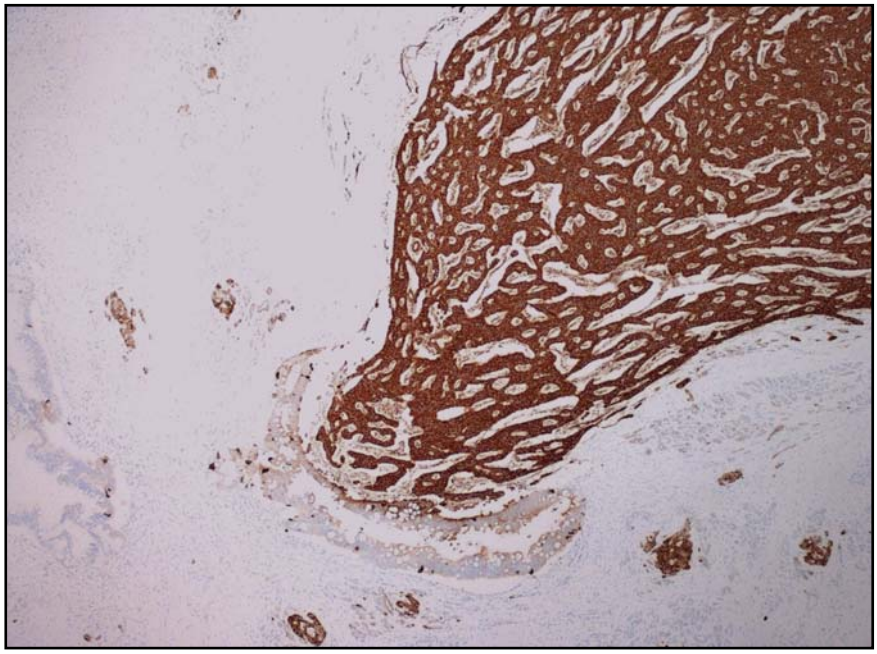

Fig. 7. Positive immunohistochemical staining of neuroendocrine tumor cells with chromogranin A; the glands of ductal carcinoma are negative (40x)

DISCUSSION

There is a significantly increased incidence of pancreatic cancer as well as neuroendocrine pancreatic tumors reported in the Slovak Republic. However, collision tumors of the pancreas are very rare. Literary data are limited only to sporadic cases of concomitant/collision tumors constituted by IPMNs and NET (Jemal *et al.* 2009, Niu *et al.* 2010; Ottenhof *et al.* 2011; Moriyoshi *et al.* 2013), solid pseudopapillary neoplasm and NET (Tewari *et al.* 2013), and cancer of the bile duct and the pancreas (Ishida *et al.* 2013). Collision tumors of the pancreas are most frequently matter of incidental and surprising finding in the histopathologic specimen. Serafini *et al.* (2017) reported the first case of collision pancreatic tumor constituted by a PDAC and neuroendocrine tumor of the pancreas, without features of IPMNs. Currently we are presenting a case of a young female patient with pancreatic ductal adenocarcinoma

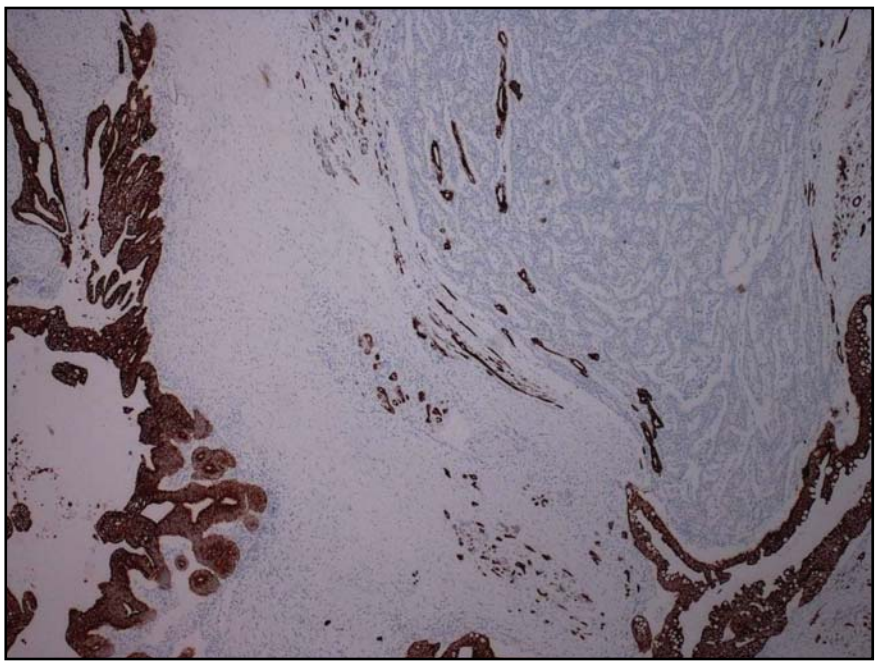

Fig. 8. Positive cytokeratin 7 immunohistochemical staining of the glands of ductal carcinoma; neuroendocrine cells are negative (40x)

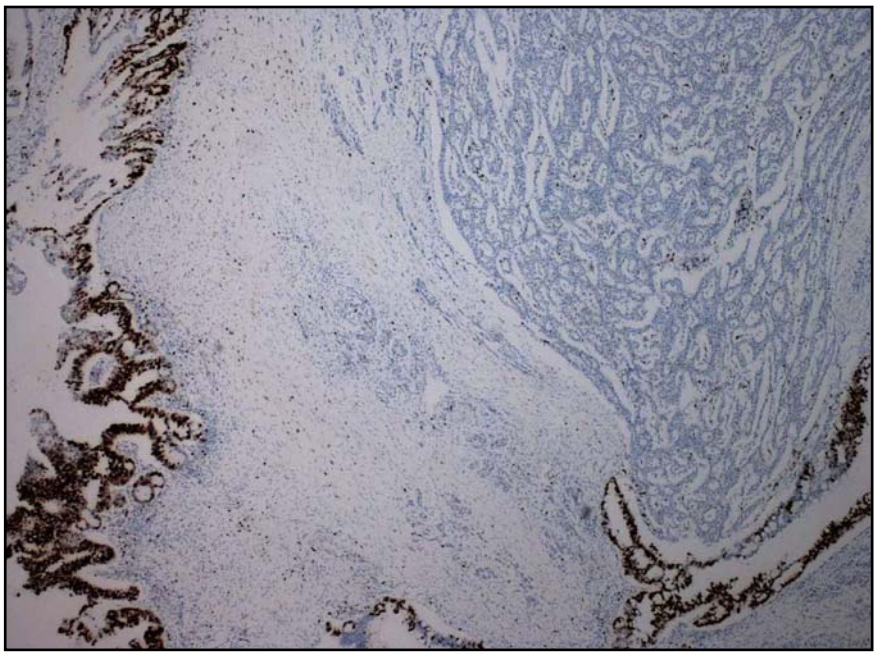

Fig. 9. Low proliferation activity labelled by Ki-67 in neuroendocrine tumor (right) and brisk activity in the cells of ductal carcinoma (left) (40x)

surrounding a smaller focal lesion of well-differentiated neuroendocrine pancreatic tumor. Collision tumors are defined as tumors located in the same organ or same anatomic site. According to the definition of the World Health Organization there is a coexistence of at least two independent cancers without mixed or transitional area (Yan *et al.* 2015). Two morphologically different malignant tumors coexist, with sharp borders in between. This entity is distinguished from that of mixed endo/exocrine lesions (mixed types) where sharp histopathologic borders between tumors are lacking and endocrine cells are combined with exocrine ones. The incidence of concomitant IPMNs and NETs has been reported in a range from 2.6 to 4.6% (Marrache *et al.* 2005; Kloppel *et al.* 2000; Izumi *et al.* 2015). There are only 3 described cases of the collision pancreatic tumor consisting of NET and PDAC in the literature (Chang *et al.* 2010; Serafini *et al.* 2017; Wang *et al.* 2018). The diagnosis of colliding tumors is most often confirmed in postoperative histopathologic

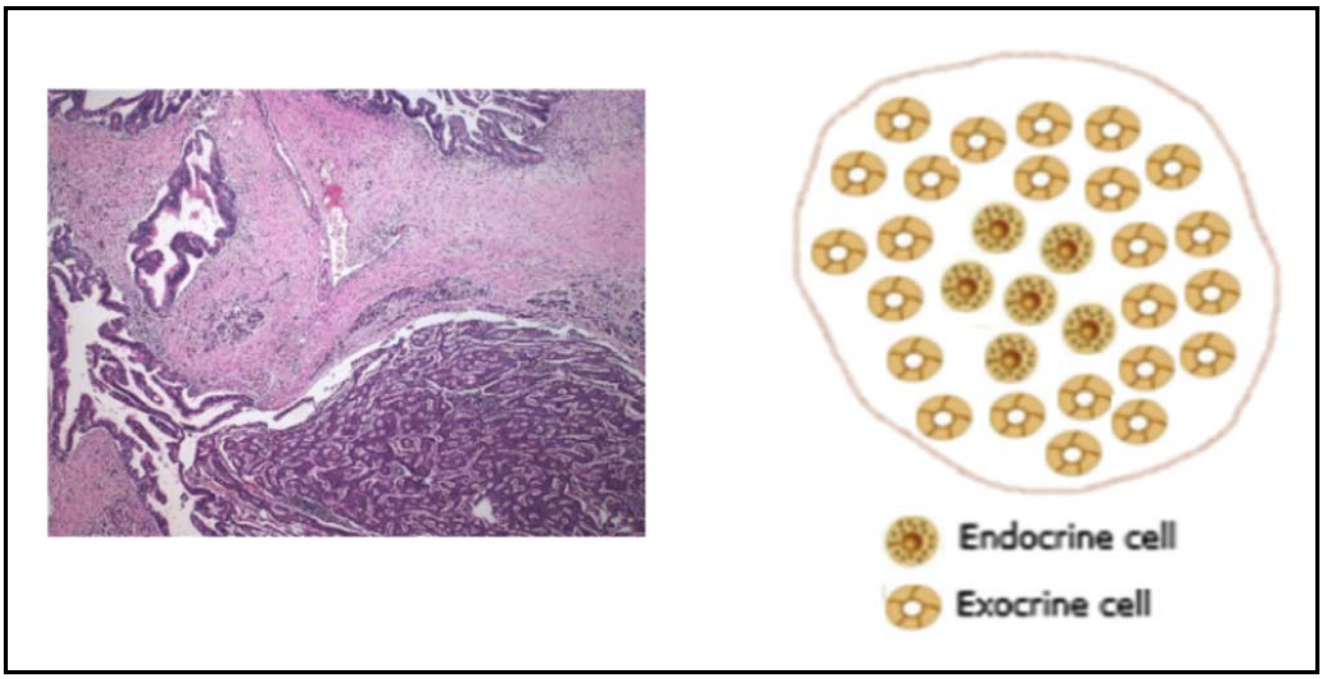

Fig. 10. Proposal of the sixth type of collision tumor: NET + PDAC. histopathologic and schematic drawing (free modified according to Chang (21))

examination of the specimen. It seems that surgical resection could be a treatment of choice for resectable cases. However, preoperative diagnosis is virtually impossible (Goh *et al.* 2006). The various combinations of collision pancreatic tumors were reported comprising the combination of PDAC and PNET (Gill *et al.* 2009), IPMN and PNET, (Niu *et al.* 2010; Moriyoshi *et al.* 2013), SPN and PNET (Tewari *et al.* 2013), hepatic carcinoid and PNET, mixed ACC and PNET or PDAC (Kim *et al.* 2013), or PDAC and biliary carcinoid (Ishida *et al.* 2013). Pancreatic tumors originate either in the exocrine or endocrine part of the gland and they are classified as ductal, acinar or neuroendocrine ones. Endocrine tumors account for less than 1-2% of all pancreatic tumors. The association between endocrine and exocrine tumors is not common. Most frequent types include mixed ductal-endocrine, mixed acinar-endocrine and mixed ductal-acinar-endocrine types of cancers. According to the WHO definition, mixed cancers contain closely mixed non separated endocrine and exocrine portions.

On the contrary, collision tumors are strictly separated. (Serafini *et al.* 2017). Goh *et al.* reported cases of colliding IPMN and small neuroendocrine tumors but without an invasive component as it was present in our case (Kloppel *et al.* 2000). Histogenesis of these colliding tumors remains unclear. However, there are several proposed theories in the literature. One hypothesis considers possible dysfunction of multiple tumor-suppressor genes that causes inadequate repair of genes, resulting in multiple types of malignancies (Capella *et al.* 2004, Jakobsen *et al.* 2016). Other theories postulate that different tumors can originate from totipotent endodermal or intermediate cells (Hashimoto *et al.* 2008). According to these hypotheses, Chang has proposed five types of coexistence of endocrine and exocrine cells: amphicrine, mixed, collision, solitary concomitant and multiple concomitant (Chang *et al.* 2010). We are currently presenting a rare case of neuroendocrine tumor that is surrounded by invasive pancreatic cancer as another possible sixth type of collision pancreatic tumor (Fig. 10). The appearance of described collision tumor was arranged with the small separated neuroendocrine tumor inside the predominant invasive pancreatic ductal adenocarcinoma. Considering simultaneous occurrence of different populations of tumor cells and histopathogenesis from pluripotent cell we could propose the new hypothesis of possible carcinogenesis sequention in terms of NET-IPMN-Invasive cancer.

CONCLUSION

PDAC is a devastating disease most frequently diagnosed at advanced stages. In general, the prognosis for the patients with collision pancreatic tumors remains as poor as for the patients with PDAC.

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DECLARATION OF ANY POTENTIAL FINANCIAL OR NON-FINANCIAL CONFLICTS OF INTEREST

The authors declare that there is no potential conflict of interest.

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