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Synchronous Pancreatic Tumours: Intraductal Papillary Mucinous Neoplasm with Pancreatic Ductal Adenocarcinoma and Neuroendocrine Tumour: A Case Presentation and Review of Literature

Diana Schlanger[1,2], Călin Popa[1,2], Ioana Rusu[3], Andrada Seicean[2,4], Nadim Al Hajjar[1,2]

[1]Surgery Department, Regional Institute of Gastroenterology and Hepatology "Prof. Dr. O. Fodor", Cluj-Napoca, Romania
[2]"Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
[3]Morphopathology Department, Regional Institute of Gastroenterology and Hepatology "Prof. Dr. O. Fodor", Cluj-Napoca, Romania
[4]Gastroenterology Department, Regional Institute of Gastroenterology and Hepatology "Prof. Dr. O. Fodor", Cluj-Napoca, Romania

*Corresponding author:
Călin Popa, MD
Surgery Department, Regional Institute of Gastroenterology and Hepatology "Prof. Dr. O. Fodor", Cluj-Napoca, Romania
E-mail: calinp2003@yahoo.com

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Rezumat

Tumori pancreatice sincrone: neoplasm mucinos papilar intraductal asociat cu adenocarcinom ductal pancreatic și tumoră neuroendocrină: prezentare de caz și review al literaturii

Tumorile sincrone pancreatice sunt tumori rar întâlnite, fiind puține cazuri publicate. Astfel, se pot aduce informații noi cu privire la stabilirea diagnosticului, managementul corespunzător şi prognosticul cazurilor. Considerăm că prezentarea acestui caz poate contribui la stabilirea unor concluzii pertinente. Prezentăm cazul unui pacient de 54 de ani, cu diagnosticul preoperator de neoplasm intraductal papilar mucinos (IPMN) cefalopancreatic, care a urmat o duodenopancreatectomie cefalică şi totalizarea pancreatectomiei în urma examenului histopatologic extemporaneu al marginii de rezecție. Diagnosticul histopatologic final a fost de IPMN cefalopancreatic asociat cu adenocarcinom ductal pancreatic (PDAC) şi cu o tumoră neuroendocrină (NET) bine diferențiată, situată la nivelul cozii pancreatice. Evoluția a fost favorabilă, fără recurență în cursul celor 3 ani de urmărire. S-a realizat un review al literaturii, în vederea ilustrării particularității cazului prezentat; acesta a identificat 4 articole despre asocierea PDAC cu NET şi 8 articole despre asocierea IPMN cu NET. Doar 2 cazuri cu cele trei tipuri de tumori pancreatice sincrone au fost identificate (IPMN, PDAC, NET). Cazul prezentat de noi discută asocierea a trei

tumori pancreatice, cu o evoluție favorabilă după pancreatectomie totală, doar alte două cazuri similare fiind raportate în literatura medicală.

Cuvinte cheie: tumori sincrone, cancer pancreatic

Abstract

Synchronous tumours of the pancreas are rare encounters, with few reported cases. Thus, new information can be brought about the diagnosis, proper management, and prognosis of cases. We believe that the presentation of this case can help to establish relevant conclusions. We report the case of a 54-year-old man, with the preoperative diagnosis of a cephalic intraductal papillary mucinous neoplasm (IPMN), who underwent a planned cephalic pancreatoduodenectomy with completion to total pancreatectomy based on the intraoperative extemporaneous histopathological examination of the resection margin. The final histopathological diagnosis was cephalic IPMN associated with invasive ductal adenocarcinoma (PDAC) and a small well-differentiated neuroendocrine tumour (NET) in the tail of the pancreas. No recurrence was detected in the 3 years of follow-up. We conducted a review of the literature to illustrate the particularities of the presented case; it identified 4 articles about the association of PDAC and NET and 8 articles regarding the association of IPMN with NET. Only 2 patients had a histopathological diagnosis of three synchronous tumours (IPMN, PDAC, and NET). We present a rare case of three synchronous pancreatic tumours, with a favourable evolution after a total pancreatectomy, only two other similar cases being reported in medical literature.

Key words: synchronous tumours, pancreatic cancer

Introduction

Intraductal papillary mucinous neoplasm (IPMN) is a cystic neoplasm of the pancreas, derived from the exocrine part of the organ. It comprises about 1-3% (1) of pancreatic exocrine tumours, being a rare encounter. The association between IPMN and pancreatic ductal adenocarcinoma (PDAC) is well-known, IPMN being considered a premalignant lesion, while around 30% of IPMNs are associated with invasive adenocarcinoma (1). The main determinant of prognosis in IPMNs is the presence of associated invasive adenocarcinoma (1).

Neuroendocrine tumours (NET) of the pancreas are relatively rare, representing only 2% of all pancreatic neoplasms (1). The prognosis in these cases depends mainly on the grade of differentiation (high-grade neoplasms have poor prognosis), as well as on the stage of the disease (1).

Givien the percentages discussed above, as well as the reported cases in medical literature, we can observe that synchronous tumours of the pancreas are extremely rare encounters (2). Finding two or more histological types of tumours inside the pancreas can either mean that there are two independent tumours or a single lesion with mixed differentiation. There are few cases reported for both types, so we have no definite conclusion regarding the prognosis and the correct management.

Pancreatic surgery consists of major interventions, with important associated risks. Therefore, knowing the correct management for each tumour, and correlating the surgical practice with the definitive histopathological diagnosis, even in relatively rare tumours, is very important for ensuring the best treatment for each patient. The prognosis of the surgical patient depends mainly on the histology of the tumour.

We present the case of a patient who under-

went total pancreatoduodenectomy, with the final diagnosis of IPMN with associated PDAC and NET. In order to highlight the particularities of the case, we conducted a review of the literature which discussed the association of PDAC or IPMN with NET in the pancreas.

Case Report

A 54-year-old man presents to our surgical department after previously being diagnosed with a pancreatic tumour in the gastroenterology department. The patient had a medical history of type 2 diabetes and high blood pressure.

On presentation, the patient complains of diffuse epigastric pain. On clinical examination, no abnormalities were found, and the blood tests were in normal ranges. The abdominal ultrasonography revealed a large tumour in the pancreatic head.

An abdominal MRI was performed, which revealed a polycystic tumour in the head of the pancreas and uncinate process, measuring 8.8/6.5/10.2 cm; dilation of the main pancreatic duct was also identified (*Fig. 1*). An endoscopic ultrasound examination was performed and revealed a cystic lesion at the level of the uncinate process, larger that 8cm diameter, presenting a wall and thickly vascularized septations, with mural nodules. After the administration of contrast agent, there was no enhancement noted. Fine-needle aspiration was performed. The cytological analysis indicates the presence of an intraductal papillary neoplasia. The preoperative diagnosis was pancreatic IPMN and surgical intervention was indicated.

After a preoperative preparation, the patient underwent surgical intervention. A cephalic pancreatoduodenectomy was initially performed as planned. Given the preoperative diagnosis of IPMN and the macroscopic evaluation of the pancreatic remnant, we decided that the resection margin should be sent for an extemporaneous histopathological examination; the resection margins were positive, focal IPMN lesions were identified. A completion to total pancreatectomy with spleen preservation was performed next (*Fig. 2*). The reconstruction was performed with a hepaticojejunostomy and a gastrojejunostomy.

The postoperative evolution was favourable, the patient spent 7 days in the high dependency unit for surveillance. The patient was discharged on the 11th postoperative day. No complications were encountered.

The definitive histopathological diagnosis revealed: a large tumour (9 x 7 x 4 cm) in the head of the pancreas with the characteristics of a mixed type (main-duct and branch-duct) IPMN with high-grade dysplasia. The IPMN had gastric and oncocytic differentiation. On the pancreatic head, a 7 mm pancreatic ductal adenocarcinoma was identified associated with the IPMN. The exocrine tumour was classified as stage 1A ($pT_1N_0M_0L_0V_0R_0$). In the tail of the pancreas, a well-differentiated neuroendocrine tumour of 6 mm diameter was found. The neuro-

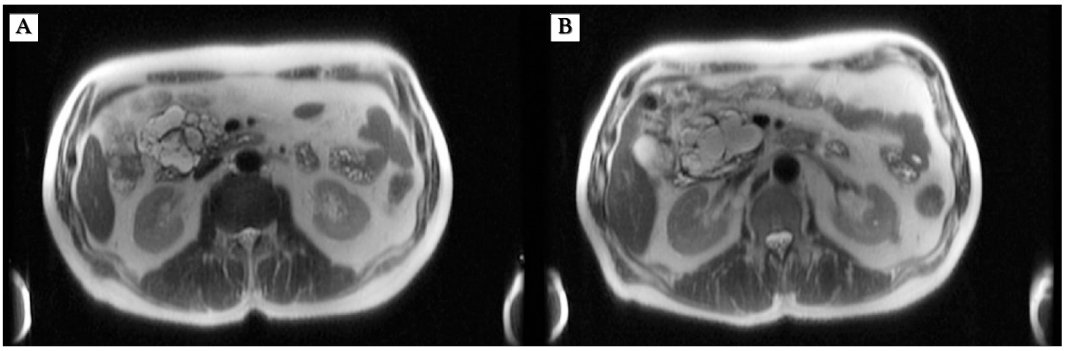


Figure 1. **(A)** Preoperative MRI, T12 section. **(B)** Preoperative MRI, T11 section

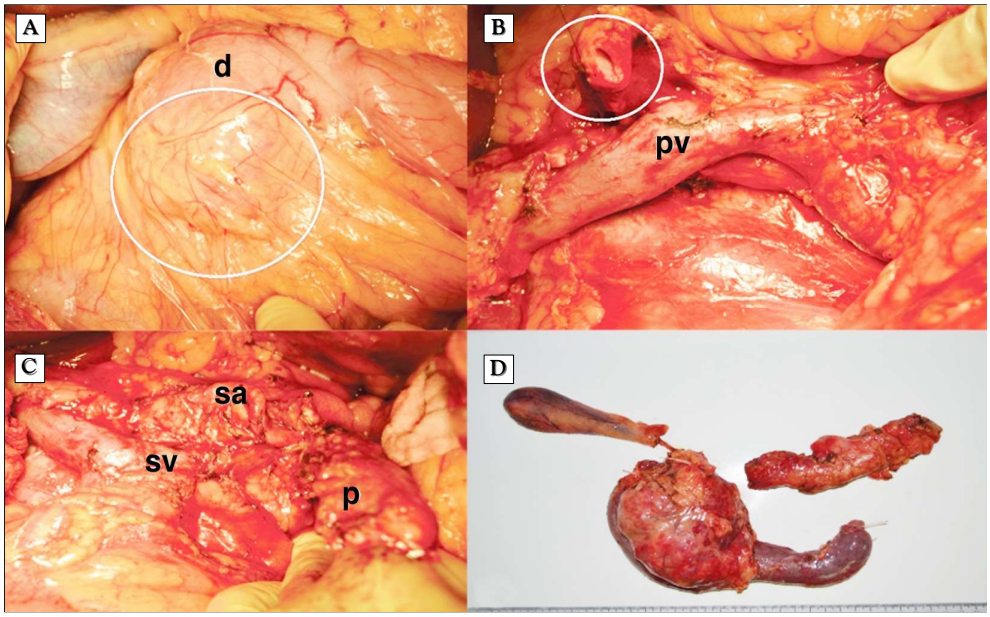


Figure 2. **(A)** Intraoperative aspect of the tumour; (**D**) - Duodenum; Circle - Pancreatic head; **(B)** Intraoperative appearance after cephalic pancreatoduodenectomy; pv - Portal vein; Circle - Pancreatic stump; **(C)** Intraoperative aspect: Completion of total pancreatectomy; sv - Splenic vein; sa - Splenic artery; p - Pancreas; **(D)** Resection specimens (cephalic duodenopancreatectomy – left and pancreatic body and tail – right)

endocrine tumour was also classified as stage 1A ($pT_1N_0M_0L_0V_0R_0$). The rest of the pancreatic parenchyma showed signs of chronic pancreatitis, as well as foci of pancreatic intraepithelial neoplasia (PanIN) (*Figs. 3, 4*).

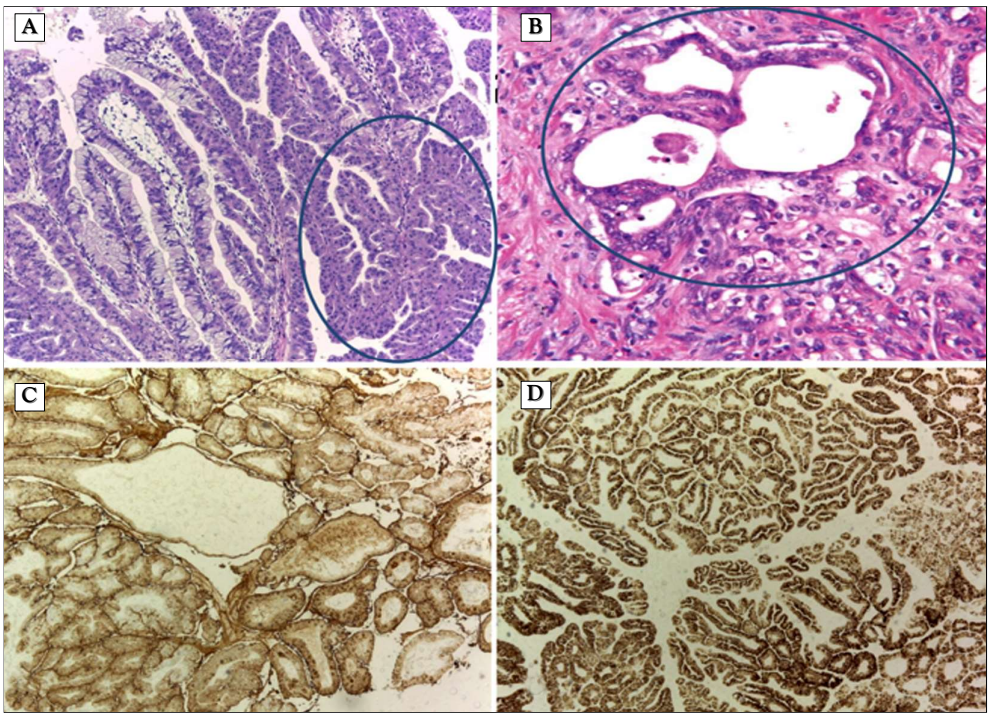


Figure 3. Histopathology - IPMN. **(A)** IPMN with high-grade dysplasia (circle); **(B)** Circle – PDAC associated with the IPMN; **(C)** Immunohistochemical Staining MUC 1; **(D)** Immunohistochemical Staining MUC 5AC

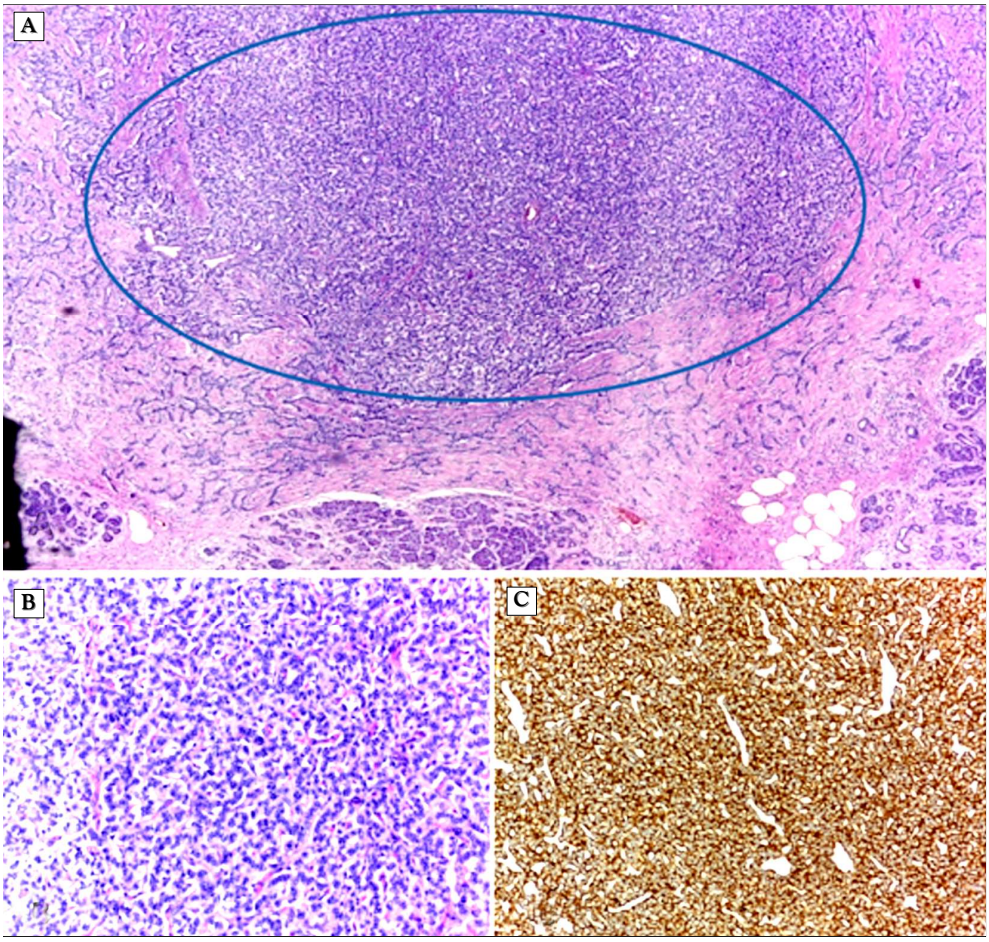


Figure 4. Histopathology– NET. **(A)** Well-differentiated neuroendocrine tumour; **(B)** Magnification image of NET; **(C)** Immunohistochemical Staining Synaptophysin Antibody

The postoperative follow-ups at 3 months, 6 months, and 1 year revealed no long-term complications (*Fig. 5*). The patient underwent adjuvant oncological treatment. Three years after surgery, there were no signs of recurrence.

Discussion

The coexistence of an exocrine and an endocrine tumour is a rare encounter, so few articles on the proposed subject can be found in the medical literature. To highlight the

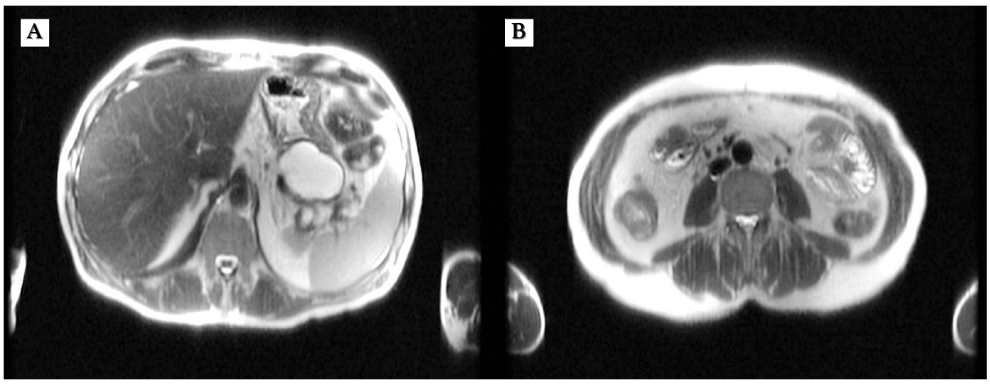


Figure 5. **(A)** 3 month check-up; **(B)** 6 month check-up - No signs of tumour recurrence.

particularity of the presented case, we did a review of the literature. Firstly, we searched the literature for articles regarding the co-existence of PDAC and NET. On the other hand, we reviewed the topic of IPMNs associated with NET. Of these articles, we tried to identify the cases similar to ours that described the synchronous appearance IPMN, PDAC, and NET.

For the first part of our review, we searched PubMed database using the following key words: "pancreatic ductal adenocarcinoma" or "PDAC" and "neuroendocrine tumour" or "NET". We identified a total of 186 articles and 6 more by citation searching. All 192 articles were screened based on their title and abstract, in order to determine the articles that were discussing the concomitant association of the two histological tumour types. Seven relevant articles were identified, but three were excluded (one was written in Japanese, one was a duplicate, and the other had no available full-text article). The remaining 4 articles were analysed based on their full text. Three articles (3-5) described cases of collision or mixed pancreatic tumours, while one article (6) described the presence of synchronous PDAC, NET, and pseudocyst.

The following table summarizes the four cases described in the articles mentioned above (*Table 1*).

If we compare the patients' characteristics presented above with our case, we can observe that epigastric pain is the central symptom registered in all cases. A total pancreatectomy was performed in 3 cases (just as in our presented case), while a pancreatoduodenectomy was performed in another case.

As we have previously mentioned, the simultaneous occurrence of exocrine and endocrine tumours in the pancreas can take various forms: we need to delineate the simultaneous presence of two different tumour types and the presence of a single tumour with mixed components. Mixed adenoneuroendocrine tumours are tumours that have a neuroendocrine and an exocrine (PDAC) component (3). A collision tumour is a malignancy that is comprised of two types of cancers in the same place, with no mixed area within the transition zone (4). All these neoplasms are rare entities, without fully understood development and evolution. Our presented case refers to separate tumours identified in the pancreas: an IPMN associated with PDAC in the head of the pancreas and an NET in the tail of the pancreas.

The preoperative diagnosis of concomitant tumours is difficult. Usually, the definitive diagnosis of mixed or synchronous pancreatic tumours is established only after the surgical intervention, on the final histopathological examination of the resection specimen. Mori et al. (3) had only diagnosed the pancreatic head tumour before surgery, the NET in the pancreatic tail being discovered during surgery

Table 1. Literature review - Case details of associated PDAC and NET

		Patient								
Study	**Year**	**Age**	**Sex**	**Symptoms**	**Preoperative evaluation**	**Fine needle aspiration**	**Preoperative diagnosis**	**Surgical intervention**	**Postoperative diagnosis**	**Evolution**
Wang et al. (4)	2018	51	F	Epigastric pain	CT EUS	Yes - NET	NET	Whipple procedure	Collision tumour PDAC-NET	No recurrence
Mori et al. (3)	2018	52	M	Epigastric pain	CT MRCP EUS	No	IPMN	Total pancreatectomy	Mixed adeno-neuroendocrine carcinoma (PDAC + NEC)	-
Ohno et al. (5)	2020	54	M	No symptoms	CT EUS	Yes - PDAC	PDAC	Total remnant pancreatectomy	Collision tumour PDAC-NET	Retro-peritoneal recurrence Bone metastasis
Liu et al. (6)	2020	74	M	Epigastric pain Poor appetite	CT MRI	No	IPMN	Total pancreatectomy and splenectomy	PDAC and pseudocyst – pancreatic body NET – pancreatic tail	No recurrence

*CT – computer tomography, MRCP – Magnetic resonance cholangiopancreatography, EUS – endoscopic ultrasonography, MRI – Magnetic resonance imaging, NET – neuroendocrine tumour, PDAC – pancreatic ductal adenocarcinoma, IPMN – Intraductal papillary mucinous neoplasm

and confirmed by the histopathological analysis. The other three case reports (4-6) also established the definitive diagnosis only on the histopathological examination of the resection specimen. In our patient, we established a preoperative diagnosis of IPMN of the pancreatic head (based on imagistic examinations and fine-needle aspiration cytology examination); on the final histopathological examination, the associated PDAC to the IPMN was described; also, the small NET (6 mm) was found in the tail of the pancreas. It is important to mention that a thorough intraoperative evaluation of the pancreas is mandatory, and any suspicion of a second tumour should be settled by an extemporaneous histopathological examination; in our case, the extemporaneous histopathological analysis changed the course of the intervention (a total pancreatectomy was performed instead of a cephalic pancreatoduodenectomy, as initially planned).

In patients with multiple pancreatic tumours, the prognosis of the case might be difficult to determine. The discussion of whether the pancreatic collision tumours have a poor or good prognosis is still ongoing, but it is generally accepted that the prognosis is determined by the stage of the PDAC (5). Our case had a favourable evolution, with good long-term survival; both tumours were resected in incipient stages.

The second part of the review of the literature intended to discuss the association between IPMNs and NET. We searched the PubMed database using the following terms: "IPMN" or "intrapancreatic mucinous neoplasia" and "NET" or "neuroendocrine tumours". We identified a total of 82 articles. We reviewed these articles based on their title and abstract and excluded 72 studies because they were not discussing patients with the concomitant association of IPMN and NET. Of the remaining 10 articles, one was in Japanese and one had no full-text article available. Therefore, 8 articles were included in our review. Six documents were case reports (7-12), one article presented a series of three cases (13), and another article was a retrospective study (14) regarding the association of IPMNs with different other pancreatic tumours (Sahora et al. identifies 5 cases of IPMN associated with NET). Analysing all the mentioned articles, we identified 14 cases of IPMNs synchronous with NET.

The *Table 2* details the cases discussed in the 6 case presentations and in the one article

Table 2. Case details of associated IPMN and NET

		Patient								
Study	**Year**	**Age**	**Sex**	**Symptoms**	**Imagistic evaluation**	**Fine needle aspiration**	**Preoperative diagnosis**	**Intervention**	**Postoperative diagnosis**	**Evolution**
Ishida et al. (7)	2012	68	F	No symptoms	CT	No	IPMN	Distal pancreatectomy	IPMN (low-grade dysplasia) + NET (G1)	No recurrence
Kadota et al. (8)	2013	74	M		CT IRM EUS	No	IPMN	Pp PD	IPMN (low-grade dysplasia) + NET (G1)	No recurrence
Tewari et al. (13)	2013	65	M	Malabsorbtion Jaundice	CT	-	-	Total pancreatectomy	IPMN + PDAC + NEC (high-grade dysplasia)	-
		79	M	Jaundice	CT	-	-	Total pancreatectomy + Splenectomy	Cholangiocarcinoma + IPMN (low-grade and high-grade dysplasia) + NET	-
		67	F	Epigastric pain	CT EUS	Yes - NET	NET	Extended distal pancreatectomy	IPMN + NET (G1)	-
Moriyoshi et al. (9)	2013	76	F	-	CT PET/CT MRCP	Yes - NET	NET	PD	Multiple tumours: NET (G1-G2) + IPMN + PDAC + adeno-neuroendocrine tumour	-
Boge et al. (10)	2017	68	M	-	IRM	-	IPMN	Total pancreatectomy	IPMN (high-grade dysplasia) + NEC	-
Costa et al. (12)	2017	56	M	Epigastric pain	CT EUS	Yes - NET	IPMN + NET	No intervention – follow-up		Stable lesions
Lena et al. (11)	2020	56	M	-	-	-	-	PD	IPMN + NET	-

*CT – computer tomography, MRCP – Magnetic resonance cholangiopancreatography, EUS – endoscopic ultrasonography, MRI – Magnetic resonance imaging, PET/CT – Positron Emission Tomography – Computed Tomography, NET – neuroendocrine tumour, PDAC – pancreatic ductal adenocarcinoma, IPMN – Intraductal papillary mucinous neoplasm, NEC – neuroendocrine carcinoma, PD – cephalic pancreatoduodenectomy, Pp PD – pylorus-preserving pancreatoduodenectomy

that comprised a series of three cases.

The association of IPMN and PDAC is well established, different percentages of association being indicated (ranging from 1.9% to 9.2%) (10). Although not as frequently encountered, the association of IPMN and NET has been recognized and reported in different studies: from 1.3% (8) of cases, 2.8% (15), 3.8% (16) to 4.6% (17) of cases. These percentages raised the topic that this encounter might be more than a simple coincidence, and a link between the two tumour types might exist.

In the *Table 2*, we can observe two patients with the final diagnosis of IPMN, associated with PDAC and NET. In one of the cases, presented by Moriyoshi et al. (9), the patient suffered from multiple endocrine neoplasia type 1 (MEN1) and multiple tumours were described in the pancreatic tissue: IPMN with invasive PDAC foci, an intraductal mixed exocrine-endocrine tumour, multiple PanNET (Pancreatic neuroendocrine tumour) and many neuroendocrine micronodules; in this case, the neuroendocrine tumours were related to the MEN1 syndrome. A cephalic pancreatoduodenectomy was performed in this patient. The other case, presented by Tewari et al. (13) described an IPMN with associated PDAC and a NEC, which also appeared to arise from the IPMN; a total pancreatectomy was performed in this case. Our case discusses a patient in which a total pancreatectomy was performed (after an extemporaneous intraoperative histopathological analysis) and the final diagnosis was an IPMN of the head of the pancreas with associated PDAC and a separate low-grade neuroendocrine tumour in the tail of the pancreas.

As we can observe from the literature review discussed above, as well as in the presented case, in most patients, the complete diagnosis was decided on the histopathological examination of the surgical resection specimen; a preoperative diagnosis is highly difficult. A preoperative diagnosis would be ideal in order to plan the appropriate surgical intervention (most synchronous pancreatic tumours might need a total pancreatectomy). In order to overcome the fact that many synchronous tumours of the pancreas cannot be diagnosed preoperatively, an adequate intraoperative evaluation is essential.

Follow-up data after surgical intervention was provided in five cases. No recurrence was detected in the cases presented by Wang et al. (4) (12-month follow-up), Liu et al. (6) (10-month follow-up), Ishida et al. (7) (three-year follow-up) and Kadota et al. (8) (18-month follow-up). One study (5) reported a retroperitoneal recurrence and bone metastasis. Our patient has been followed for three years, no recurrence has been detected, and his evolution is favourable.

The synchronous appearance of different histological types of pancreatic tumours is a rare encounter, especially when some of the discussed tumours, like IPMNs and NETs, are rare pancreatic tumours on their own. Case presentations in these situations help to identify the best management of the patient, adapted to its characteristics, in order to offer each patient a personalized, yet complete evaluation and treatment (18).

Conclusions

Synchronous pancreatic tumours, especially an association between three different histological types are rare encounters and particular cases.

The preoperative diagnosis is highly difficult to determine, and the patient should be very well investigated when the suspicion of pancreatic tumours exists.

The right treatment should be chosen carefully, and a thorough intraoperative examination of the pancreas is essential; an extemporaneous histopathological examination should be performed to confirm or rule out any suspicion.

The prognosis of these cases is yet to be determined, being decided by the biological behaviour of the multiple tumours. A close follow-up of the patient is recommended.

Conflict of Interest

The authors declare no conflicts of interests.

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