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Letter to editor

Not all pancreatic cystic lesions are the same: lesson from a case with three different coexisting neoplasms

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Summary
An asymptomatic 79-year old woman presented with a 40 mm pancreatic cystic lesion, located in the pancreatic body-tail and consistent with branch-duct intraductal papillary mucinous neoplasm (BD-IPMN) without "high risk stigmata". During a 4-year follow-up period, imaging showed no mural nodules or main pancreatic duct dilation, and serum CEA and CA19.9 were within normal range. Later, computed tomography showed a rapid increase in cyst size up to 59 mm, which led to a clinical suspicion of malignant transformation. The patient underwent distal pancreatectomy, and final histology revealed the presence of three distinct pancreatic neoplasms: serous cystadenoma (SCA), BD-IPMN, and well-differentiated G1 neuroendocrine tumour (PanNET-G1). The co-occurrence of pancreatic neuroendocrine and exocrine tumours is exceedingly rare. To the best of our knowledge, this is the first reported case of the concomitant presence of three different pancreatic tumors in the same pancreatic specimen arose adjacent one to each other within the same macroscopic lesion.

Key words: pancreatectomy, pancreatic intraductal neoplasms, pancreatic neoplasms, pancreatic cyst

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Dear Editor,
although the association between pancreatic exocrine and neuroendocrine neoplasms has already been reported in literature, we would like to report the first case, to our knowledge, of the concomitant presence of IPMN, NET and SCA in the same specimen, with the last two neoplasms within in the same cystic lesion.
In August 2016, a 79-year-old Caucasian woman with a history of previous breast cancer was found to have a 40 mm cystic lesion in the body-tail region of the pancreas during follow-up ultrasonography. The patient was asymptomatic and did not refer previous pancreatitis or familial history of pancreatic ductal adenocarcinoma. The patient was referred to our Surgical Unit in June 2017. Computed tomography (CT) scan and magnetic resonance cholangio-pancreatography (MRCP) both showed multiple and diffuse pancreatic cystic lesions. Multiple liver and kidney cysts and a 15 mm in size gallbladder polyp, with a slight contrast enhancement, were also detected. Based on these findings the clinical suspicion was a multiple BD-IPMN without "high risk stigmata" while presenting "worrisome features", according to Fukuoka guidelines[1].
The patient underwent close surveillance with MRCP and endoscop-

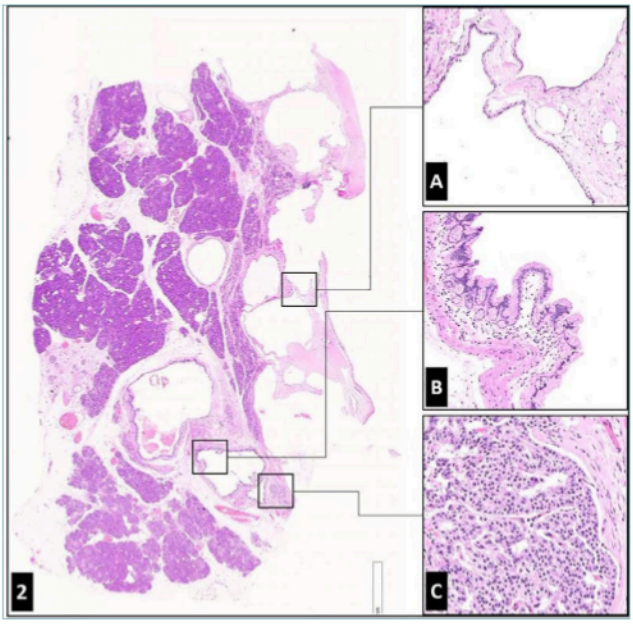

Figure 1. Representative picture of the haematoxylin and eosin stain. Inserts are showing the three different neoplastic lesions co-occurring within the pancreatic parenchyma: a serous oligocystic cystadenoma (A, top panel), a gastric-type low-grade intraductal papillary mucinous neoplasm (B, middle panel), and a neuroendocrine microadenoma (C, lower panel).

ic ultrasound. During the first 2 years of surveillance, imaging showed no mural nodules or main pancreatic duct dilatation. The growth rate of the main cystic lesion was less than 5 mm/2 years (45 vs. 42 mm), and the cystic lesion in the pancreatic body was 7 mm in size, with a clear communication with the main pancreatic duct. The patient remained asymptomatic, and serum biochemical tests and tumor markers (CEA and CA19.9) were within the normal range. In July 2019, a MRCP detected an increase in size of the IPMN in the pancreatic tail (55 mm vs 45 mm), without any dilation of the main pancreatic duct. In February 2020 a CT scan showed further enlargement of the IPMN in the pancreatic tail (59 vs. 55 mm), and of the other cystic lesion in the pancreatic body (12 vs 7 mm). Tumor markers were within the normal range. A possible malignant transformation of BD-IPMN was suspected, based on a tumor size greater than 3 cm, and rapid growth, both of which represent "worrisome features" according to revised Fukuoka guidelines [1]. Finally, in July 2020 the patient underwent distal pancreatectomy with splenectomy. Gross examination of the specimen showed a solitary, 40 mm in size, multiloculated pancreatic lesion with a serous content. Unexpectedly, microscopic examination revealed the coexistence of three different pancreatic tumors: macrocystic SCA and a gastric type incipient IPMN with low grade dysplasia and a 2.5 mm non-functioning PanNET G1 (Fig. 1). Examination of NET revealed a Ki-67 labelling index of 0.1% and a mitotic index of 0/2 mm^2. Immunohistochemistry analysis of SCA showed a positive staining for cytokeratin AE1/AE3 and inhibin, whereas synaptophysin, chromogranin, CD10, CEA and PAX 8 stained negative.

Pancreatic cystic neoplasms include a broad range of tumors with varying degrees of benign, borderline or malignant behavior. Preoperative differential diagnosis between SCA, IPMN and other mucinous neoplasms can be challenging, especially for larger pancreatic cystic neoplasms located in the tail of the pancreas where a communication with the ductal system might be difficult to detect. In such cases, additional features, like tubular structure and the presence of multiple cystic lesions along the pancreas, can help in distinguishing IPMN from serous or mucinous neoplasms [2].

Cyst size alone is not a sufficient criterion for resection in IPMNs, although larger cysts are associated with increased risk of high-grade dysplasia and malignant transformation [1,3]. Thus, indications for surgical resection of BD-IPMN consider several factors, such as patient's age, comorbidity, cyst location and risk of malignancy [1]. In our case, the absence of main pancreatic duct dilatation or other malignant features (e.g. enhancing mural nodules, thickened cystic walls, elevated neoplastic markers, jaundice, duct dilatation) led to close clinical surveillance, according to revised Fukuoka consensus guidelines of 2017 [1]. Distal pancreatectomy and splenectomy were performed only when a rapid cyst growth occurred after a 3-year "wait and see" approach.

Association of exocrine neoplasm and neuroendocrine neoplasms is exceedingly rare. In 1993 Heresbach et al. first reported the association of a cystadenocarcinoma of the head of the pancreas with SCA and NET of the pancreatic body [4]. Subsequently, other authors described the occurrence of different pancreatic tumors, and frequent combinations include SCA with NET, or IPMN with NET. The association of three different tumor types is even more rare [5,6]. To best of our knowledge, our case is the first report of concurrent IPMN, SCA and NET within the same pancreatic lesion.

Serous cystadenoma is an uncommon non-mucinous cystic neoplasm, with a benign behavior except for a few malignant reported cases in the literature. When non-symptomatic, SCA can be managed with a "wait and see" policy [7]. It typically occurs as a sporadic lesion in elderly females with rare cases in hereditary disorders, like Von Hippel Lindau (VHL) disease. Hsieh et al. reviewed 14 cases of simultaneous SCA

and NET up to 2009 [8]. Three cases were associated with VHL, while the remaining 11 cases were sporadic, with a female predominance in both groups [8]. As reported by Hammel et al. pancreatic involvement is common in VHL disease: 77% of patients showed a pancreatic involvement; it consisted in SCA and in NET in 12.3% of cases, respectively, and 11.5% of patients had a combination of both lesions [9]. In the present case, the patient did not receive genetic testing for VHL syndrome or other hereditary tumor syndromes, because the criteria for genetic testing were not met (no positive family history or VHL-like lesions).

Despite rare findings, the majority of NET are sporadic and non-functioning; almost all reported IPMN and NET combinations revealed low grade dysplasia in IPMN. Recently, Schiavo Lena et al. [10] found a common cell origin in a case of mixed IPMN and NET; both tumors shared amplification of the *CCND1* gene and the same *KRAS, GNAS* and *CDKN2A* mutations, proving clonality. Further studies are needed to establish similarities in molecular and genetic pattern among different tumor types.

The case reported herein highlights the possibility of multiple synchronous pancreatic neoplasms, presenting with similar clinical features, while arising from different lineages and having different biological behaviour. Few cases of concurrent exocrine and neuroendocrine neoplasms are reported in the literature, and information concerning the pathogenesis of these tumor combinations and the prognosis is still lacking. Clinicians should be aware of the possibility of synchronous pancreatic neoplasms, and perform an oncological pancreatic resection with curative intent.

Conflicts of interest statement

The authors declare no conflicts of interest.

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Authors' contributions

Conceptualization, M.F. and C.P.; writing—original draft preparation, A.C.M. and A.S.T.; figure preparation, M.F. and A.C.M.; writing—review and editing, A.C.M., V.A., M.F. and C.P. All authors have read and agreed to the published version of the manuscript.

Ethical consideration

The information contained in this manuscript complies with the journal's ethical standards. Written informed consent was obtained from the patient for study participation and data publication.

References

1 Tanaka M, Fernández-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology 2017;17:738-753. https://doi.org/10.1016/j.pan.2017.07.007

2 Lévy P, Rebours V. Differential Diagnosis of Cystic Pancreatic Lesions Including the Usefulness of Biomarkers. Visc Med 2015;31:7-13. https://doi.org/10.1159/000371786

3 Tanaka M. International consensus on the management of intraductal papillary mucinous neoplasm of the pancreas. Ann Transl Med 2015;3:286. https://doi.org/10.3978/j.issn.2305-5839.2015.11.09.

4 Heresbach D, Robert I, Le Berre N, et al. Cystic tumors and endocrine tumor of the pancreas. An unusual association. Gastroenterol Clin Biol 1993;17:968–971.

5 Schlanger D, Popa C, Rusu I, et al. Synchronous Pancreatic Tumours: Intraductal Papillary Mucinous Neoplasm with Pancreatic Ductal Adenocarcinoma and Neuroendocrine Tumour: A Case Presentation and Review of Literature. Chirurgia (Bucur) 2021;116:1-9. https://doi.org/10.21614/chirurgia.116.eC.2425

6 De Marchi G, Paiella S, Luchini C, et al. A rare case of three different tumors in the same pancreatic specimen: a case report and brief review of the literature. J Gastrointest Oncol 2016;7:e52-e57. https://doi.org/10.21037/jgo.2016.01.04

7 Bassi C, Salvia R, Molinari E, et al. Management of 100 Consecutive Cases of Pancreatic Serous Cystadenoma: Wait for Symptoms and See at Imaging or Vice Versa? World J Surg 2003;27:319-323. https://doi.org/10.1007/s00268-002-6570-7

8 Hsieh M-S, Liu K-L, Tien Y-W, et al. Combined Pancreatic Endocrine Tumor and Serous Cystadenoma. J Formos Med Assoc 2009;108:739-745. https://doi.org/10.1016/S0929-6646(09)60399-5

9 Hammel PR, Vilgrain V, Terris B, et al. Pancreatic involvement in von Hippel-Lindau disease. The Groupe Francophone d'Etude de la Maladie de von Hippel-Lindau. Gastroenterology 2000;119:1087-1095. https://doi.org/10.1053/gast.2000.18143

10 Schiavo Lena M, Cangi MG, Pecciarini L, et al. Evidence of a common cell origin in a case of pancreatic mixed intraductal papillary mucinous neoplasm–neuroendocrine tumor. Virchows Arch 2021;478:1215-1219. https://doi.org/10.1007/s00428-020-02942-1