Cystic Lesions of the Pancreas - Expect the Unexpected: Co-Occurence of a Mixed Duct-Type Pancreaticobiliary IPMN and a Microcystic Serous Cystadenoma - A Case Report

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Abstract

Background: Cystic lesions of the pancreas are a heterogeneous group of lesions. With the wider use of routine abdominal cross-section analyses these lesion are identified at an increasing frequency. The majority of lesions, including serous cystadenomas, are benign and often can be treated using a conservative approach. However, a subset of cystic lesions of the pancreas, including intraductal papillary mucinous neoplasms represent a pre-malignant condition and need surgical intervention. The correct interpretation of pre-therapeutic images and intra-operative presentation of these lesions is fundamental in order to choose the correct treatment modality.

Case Presentation: Here we describe the case of a 75-year old female patient with an ambigous cystic lesion of the pancreas, which presented in imaging exams as main duct IPMN with complete cystic transformation of the pancreatic main duct and a second cystic lesion in the pancreatic tail. Intraoperatively, in addition to the IPMN, the tumorous lesion of the pancreatic tail was resected en-bloc with intraoperatively frozen section analysis revealing a microcystic serous cystadenoma. Histologically the lesion was composed of a mixed duct-type pancreaticobiliary IPMN of the entire pancreatic gland, co-ocurring with a microcystic serous cystadenoma located in the pancreatic tail, raising intraoperative concern for the presence of invasive carcinoma. NGS analyses revealed that these two co-ocurring lesions were genetically not related and presented a collision tumor.

Conclusion: Cystic lesions of the pancreas are a heterogeneous group of lesions with different biologic behavior. Given the high morbidity and mortality rates for surgical procedures involving the pancreas, surgery should only be performed, if local symptoms occur or the lesion has malignant potential. Therefore, a correct pre-operative and possibly intra-operative diagnosis is essential in the management of cystic lesions of the pancreas. Here we demonstrate that i) cystic lesions of the pancreas with different biologic behavior can co-occur in the same patient, ii) that pre-therapeutic imaging can differ significantly from histology and intraoperative findings, and iii) that these complex cystic lesions are best addressed using interdisciplinary approaches involving experienced radiologists, surgeons, pathologist and other care-givers, in order to provide adequate subsequent clinical management.

Keywords: Case report; Cystic lesions; Interdisciplinary management; Pancreas

Introduction

With the advent of better imaging technologies and the wide-spread use of abdominal cross-sectional imaging, cystic lesions of the pancreas are identified at an increasing frequency. Both, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) suggest that about 2.5-5% of all patients undergoing routine imaging are found to have pancreatic cysts [1,2]. Cystic lesions of the pancreas, comprising neoplastic and non-neoplastic lesions, however, are an extremely heterogeneous group of lesions [1]. The majority of cystic lesions are non-neoplastic inflammatory pancreatic pseudocysts, and true cystic neoplasms represent only about 15-20% of all pancreatic cysts. Importantly, some neoplastic lesions are malignant (e.g. cystic transformation of invasive cancer) or harbor significant potential of malignant transformation (i.e. precursor lesions of invasive cancer), hence the diagnosis of a cystic lesion of the pancreas may not only be a source of significant angst for both, the patient and his/her caregiver, but more importantly, the adequate clinical management of cystic lesions of the pancreas strongly depends upon the correct pre-therapeutic diagnosis [1,3,4] (Figure 1).
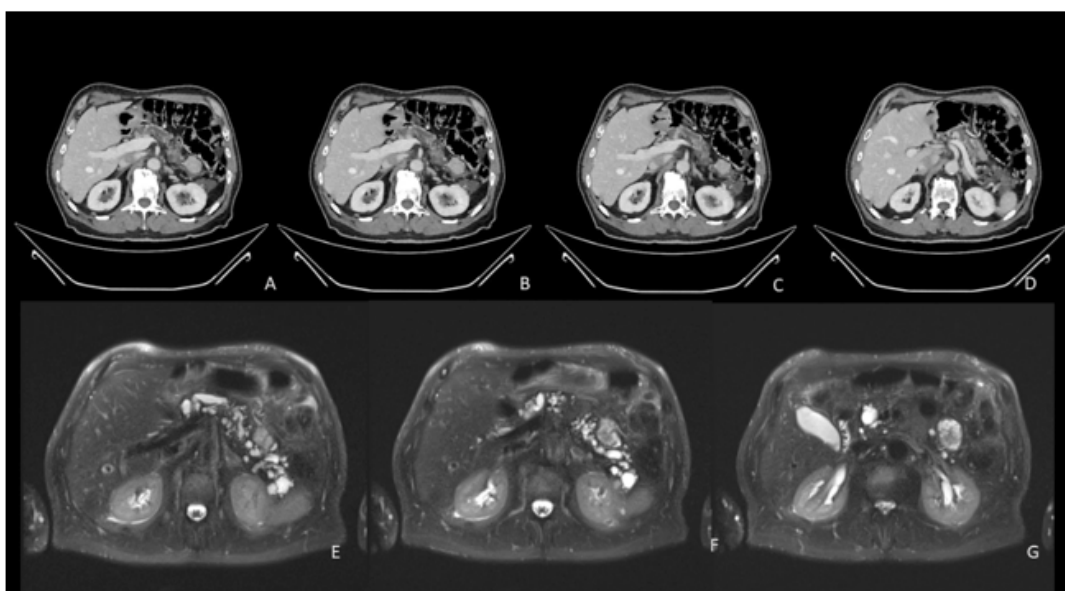
Figure 1: Preoperative imaging: CT scan **(A-D)**, MRI results showing the multi-cystic lesion of the entire pancreas **(E-G)**.

Intraductal Papillary Mucinous Neoplasm (IPMN) of the pancreas is a grossly visible intraductal epithelial neoplasm of mucin-producing cells, arising in the main pancreatic duct (main duct-type) and/or its branches (branch duct-type) or in both combined (mixed duct-type) [5-8]. Clinical symptoms for main-duct type IPMNs include epigastric pain, chronic pancreatitis, weight loss, diabetes mellitus and jaundice, whereas branch duct-type IPMNs are often detected incidentally [4,5]. Histologically there are three different types of IPMN, based on the predominant cell differentiation pattern (gastric-type (70%), intestinal-type (20%) and pancreaticobiliary-type IPMN) and protein expression [9] (Table 1; adopted from WHO classification and modified according to immunohistochemistry used for the case [9]).

A two-tiered grading system is applied for IPMNs differentiating between low-grade and high-grade IPMN, with the latter being characterized by complex architectural features and severe cytologic atypia [9]. Table

Gastric-type IPMNs most frequently display low-grade atypia, whereas intestinal-type IPMNs (about 20% of all IPMNs) and pancreaticobiliary IPMNs most often display high-grade atypia and invasive carcinoma, which can occur in the area of IPMN (IPMN with associated carcinoma) or non-contiguous (IPMN with concomitant carcinoma) [9]. Although there may be focal growth of IPMN limited to a portion of the gland, the whole pancreas is at risk for the development of malignancy, the so called "field defect" [10-14]. In general, irrespective of type of carcinoma and IPMN, invasive carcinoma is identified in about 60% of main-duct type IPMNs [9]. There are no well-established etiological factors for IPMNs and the pathogenesis of IPMNs is unknown [9]. IPMNs often harbor somatic *KRAS* mutations (60-80%) and *GNAS* mutations (50-70%) [15,16]. P53 overexpression, indicating missense mutations of *TP53* are detected in 10-40% of high-grade IPMNs and 40-60% of invasive carcinomas associated with IPMNs. Loss of SMAD4 usually occurs in the context of invasion [9].

IPMNs without invasive carcinoma are often curable by surgery, whereas IPMNs with invasive carcinoma show the prognosis of the respective associated invasive component [4,9].

Serous Cystadenomas (SCA) of the pancreas, in contrast, are benign cystic epithelial neoplasms accounting for 1-2% of all pancreatic neoplasms and 16% of all resected pancreatic cystic lesions and most frequently arise in the body or the tail of the pancreas [9,17]. Most patients with SCA are asymptomatic, and patients are diagnosed incidentally by routine abdominal imaging. Microcystic Serous Cystadenomas (MSCA) account for 45% of the cases and are usually well-circumscribed and composed of multilocular microcysts (measured in millimeters), presenting with a typical honeycomb pattern on gross examination/imaging. Despite typical radiographical appearance, misdiagnosis for SCA based on preoperative imaging is high [18,19]. In particular oligo- and macrocystic appearance, which can be found in about 10% of SCA can cause difficulties in differentiating them from mucinous cystic neoplasms [4].

There are no known etiological factors for SCA, however some cases are associated with Von Hippel-Lindau Syndrome (VHL) and about 90% of patients with VHL develop serous cystadenomas. Furthermore, somatic *VHL*-Gene mutations have been found in sporadic cases [20]. However, the exact pathogenesis remains largely unknown [9,20]. In contrast to IPMNs, prognosis of patients with serous cystadenomas is excellent and surgical resection is only indicated in cases where local symptoms become disturbing, or for cases that show locally aggressive features [4,9]. Pretherapeutic cytologic and histologic evaluation of pancreatic lesions is one of the most difficult challenges in pancreatic diagnostic evaluation [21]. Despite a high diagnostic accuracy rate in diagnosing solid pancreatic lesions, the evaluation of cystic lesions remains challenging. One major impediment is the limited yield of cellular material for additional ancillary studies.

However, the increased knowledge of underlying molecular mechanisms of these lesions in combination with the advent of advanced molecular pathology technologies, (next generation sequencing, digital droplet PCR etc.) has enabled us to apply new methods that will potentially enable us to better predict the biologic behavior of cystic pancreatic lesions. For a comprehensive review see reference [22]. In general, studies have tried to evaluate the necessity for surgical resection of cystic lesions of the pancreas and guidelines for the management of pancreatic cysts have been formed to assist in clinical decision making, however not for all cases these guidelines are applicable [23,24]. Here we present the very rare case of a 75 year-old patient presenting an ambiguous lesion and intraoperatively raising the concern for invasive carcinoma.

Case Presentation

Patient Information, Clinical Findings, Diagnostic Assessment and Therapeutic Intervention

The 75-year-old male patient had presented at his local family consultant as part as a routine follow-up check-up 10 years after treatment of an adenocarcinoma of the prostate. The patient had no complaints/symptoms; there was no family history of malignancies. Physical examination revealed no important clinical findings and the patient underwent Ultrasound Examination (USE) as part of the routine clinical check-up for his prostate carcinoma, where a cystic lesion of the pancreas and an enlarged pararectal lymph nodes were found incidentally using PSMA-Positron Emission Computet Tomography (PSMA-PET CT). The patient was referred to our pancreas centre, where a pancreas Magnetic Resonance Imaging (MRI)/Magnetic Resonance Cholangiopancreatography (MRCP) was carried out, in which a main-duct IPMN of the entire pancreas was visible, with dilatation of the main pancreatic duct to a maximum of 1.3 cm. In addition, a second lesion was detected in the area of the pancreatic tail, which could not be further classified at this time point.

A thoracic and abdominal CT was performed to complete the staging and exclude metastases. Subsequently, the case was discussed in our interdisciplinary tumor conference where a primary total pancreatectomy was recommended. Under the suspicion of a possible malignant transformation of the main duct IPMN into an invasive pancreatic carcinoma, the treatment of the pelvic lymph node was postponed. We performed an open total spleen-conserving pancreatectomy with biliodigestive anastomosis and gastroenterostomy in our surgical center. The intraoperative findings confirmed the imaging results showing a complete transformation of the main pancreatic duct with multiple cysts, and the ambiguous lesion described in MRI and CT was found in the pancreatic tail (Figure 2). Hence, after successful *en-bloc* resection, the specimen was sent for an intraoperative frozen section examination to exclude a malignant tumor, which would have resulted in subsequent splenectomy and lymph node dissection.

Follow-up and Outcomes

The postoperative course of the patient was without complications, with a 10-day hospital stay including one day monitoring at the intensive care unit. The patient received insulin substitution training and detailed nutritional advice on the substitution of pancreatic enzymes during his inpatient stay.

Histopathology Findings

The macroscopic examination revealed a large multi-cystic lesion involving the entire pancreatic resection specimen with cystic spaces up to 1 cm in diameter filled with mucinous fluid. The main duct and the branch ducts were equally involved and dilated (Figure 2). The remaining pancreatic tissue showed a firm grey cut surface with only focal maintained regular lobulation. Furthermore, the tail of the pancreas showed a nodular bulging lesion, which appeared to be an isolated well-circumscribed lesion with a typical honeycomb appearance composed of small (max 0.3cm) cystic spaces filled with clear serous fluid (Figure 2). In the center of the lesion, a star like-scar could be seen (Figure 2).
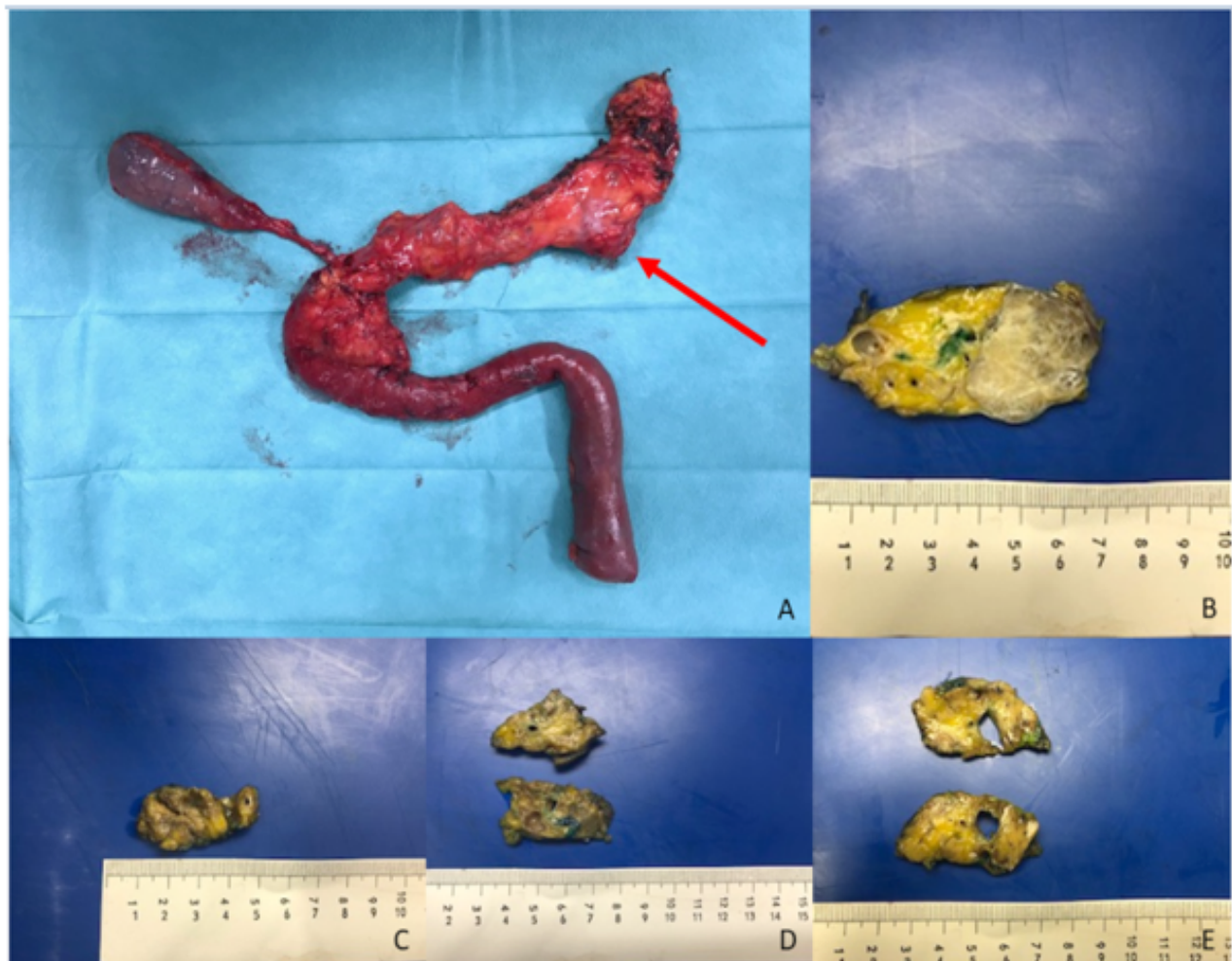
Figure 2: Macroscopic findings: Operation specimen sent to intraoperative evaluation using frozen section **(A)** and macroscopic presentation after formalin fixation (from tails to head) showing cystic dilation of the main duct **(B-E)** and branch ducts and the typical macroscopic presentation of the microcystic serous cystadenoma in the tail of the pancreas **(B)**.

Histologically the main and branch duct-involving cysts were lined by simple, columnar, mucin-filled epithelial cells with retained nuclear polarisation and showed only focally moderate folding of the epithelial lining with pseudostratified nuclei (Figure 3). One area however displayed more complex micropapillary structures, loss of polarity and irregular hyperchromatic nuclei with nucleoli (Figure 3). Even after extensive sampling of the pancreatic tissue, no invasive carcinoma could be detected. Immunohistochemistry revealed a strong positivity for MUC1, MUC5AC and MUC6 and negativity for CDX2 and MUC2 suggesting a pancreaticobiliary IPMN (Table 1) (Figure 3). The lesion in the tail, which had temporarily caused intraoperative concern for invasive carcinoma was composed of small microcystic spaces lined by a single layer of flat to cuboidal cells with clear cytoplasm and small nuclei with dense homogeneous chromatin; no nuclear atypia or mitoses were seen (Figure 4).
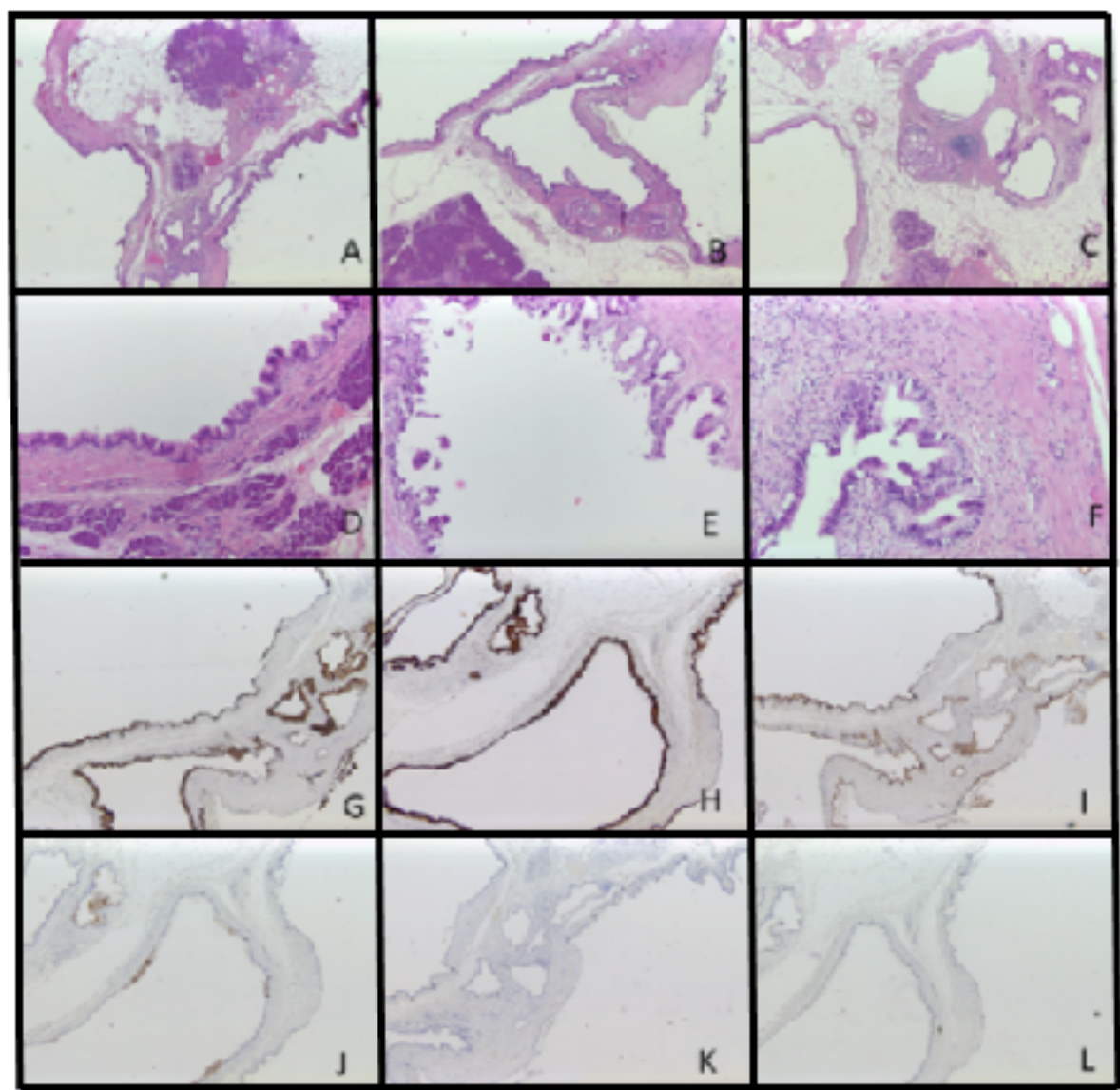
Figure 3: Microscopic findings and immunohistochemistry of IPMN component: 2.5x magnification of IPMN depicting involvement of main duct (arrow) and branch ducts **(A-C)**. The majority of the epithelial linings showed moderate folding and monomorphous cells with nuclei with retained polarization **(D)**. Focal high-grade dysplasia **(E-F)**. Positive immunostains: MUC5AC **(G)**, MUC1 **(H)**, MUC6 **(I)** and CEA **(J)**. Negative stainings for CDX2 **(K)** and MUC2 **(L)**.

Immunohistochemistry	MUC1	MUC2	MUC5AC	MUC6	CDX2	CEA
IPMN						
Gastric-type	-	-	+	-/+	-	-
Pancreaticobiliary-type	+	-	+	+	-	+
Intestinal-type	-	+	+	-	+	+

Table 1: Immunohistochemistry used to differentiate between IPMN subtypes.
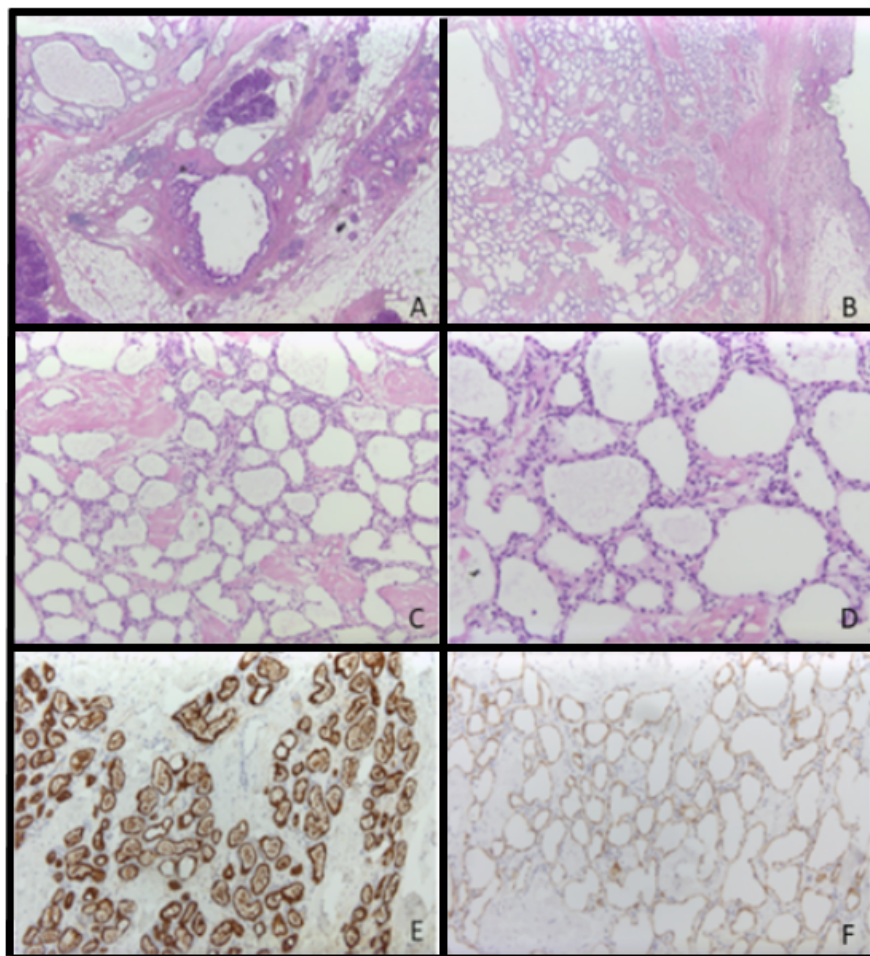
Figure 4: Histomorphology and immunohistochemistry of SCA: The IPMN and the microcystic serous cystadenoma (arrow) are located in the tail of the pancreas **(A,B)**. Close up of the cystic epithelial lining shows flat monomorphous epithelial cells with centrally located round nuclei (**(B)** = 10x magnification, **(C)** = 20x magnification).

Molecular Pathology

Microdissection of the two tumors was performed and DNA was extracted separately and sequenced using next generation sequencing. As expected, the IPMN showed an activating *KRAS* mutation and a mutation of *KEAP1* with yet unknown biologic significance (Table 2). The cystadenoma did not reveal any mutation in the genes analyzed indicating that the two lesion are not genetically related, but rather represent a collision tumor (Table 3). The case was signed out as mixed duct-type pancreaticobiliary IPMN involving the entire pancreas with focal high-grade dysplasia, co-occurring with a benign microcystic serous cystadenoma of the pancreatic tail; no signs of invasive carcinoma. Five months after the procedure the patient is alive and well.

Gen	Exon	Codon	Mutationssatus
BRAF	15	582-612	Wildtyp
DDR2	4-19	1-856	Wildtyp
ERBB2	8, 19-22	302-338, 737-883	Wildtyp
HRAS	2-4	1-93, 98-150	Wildtyp

KEAP1	2-6	1-625	EX3: c.1122G>C p.L374F
KRAS	2-4	1-73, 98-150	EX2: c.[35G>A], p.[G12D] c.[35G>T] p.[G12V]
NFE2L2	2	16-104	Wildtyp
NRAS	2-4	1-37, 41-92, 98-150	Wildtyp
PIK3CA	2, 5, 8, 10, 21	58-117, 304-353, 418-468, 514-554, 980-1069	Wildtyp
PTEN	1-9	1-404	Wildtyp
PHOA	2, 3	1-92	Wildtyp
TP53	5-9	126-331	Wildtyp

Table 2: Sequencing results for the IPMN component.

Gen	Exon	Codon	Mutationssatus
BRAF	15	582-612	Wildtyp
DDR2	4-19	1-856	Wildtyp
ERBB2	8, 19-21	302-338, 737-883	Wildtyp
HRAS	2-4	1-93, 98-150	Wildtyp
KEAP1	2-6	1-625	Wildtyp
KRAS	2-4	1-73, 98-150	Wildtyp
NFE2L2	2	16-104	Wildtyp
NRAS	2-4	1-37, 41-92, 98-150	Wildtyp
PIK3CA	2, 5, 8, 10, 21	58-117, 304-353, 418-468, 514-554, 980-1069	Wildtyp
PTEN	1-9	1-404	Wildtyp
PHOA	2, 3	1-92	Wildtyp
TP53	5-9	126-331	Wildtyp

Table 3: Sequencing results for the serous cystadenoma component.

Discussion

Cystic lesions of the pancreas are a heterogeneous group of lesion comprising non-neoplastic and neoplastic lesions. Importantly, a subset of these lesions, including IPMNs, are premalignant lesions that can be associated with invasive carcinoma and therefore need surgical intervention [1,4]. SCAs in contrast belong to the group of benign cystic lesions and, if possible, a conservative approach is recommended, taking into account postoperative morbidity and mortality [4,24]. As more and more cystic lesions are diagnosed during clinical routine examinations, a correct pre-therapeutic diagnosis is required in order to make the right treatment choices. Normally, diligent and experienced examiners are capable of giving the right diagnosis based on imaging only, however, some cases present as ambiguous lesions and need more complex diagnostic approaches.

Here we present the very rare case of a pancreatic mixed duct-type pancreaticobiliary (focal) high-grade IPMN involving the entire pancreas co-occurring with a microcystic serous cystadenoma of the pancreatic tail [9]. Due to the advanced main duct IPMN, a total pancreatectomy was planned in advance. The risk of a malignant tumor in the tail of the pancreas was considered even though the imaging criteria for invasive carcinoma were not fully met, as the diagnosis of an invasive malignant tumor in the tail of the pancreas would have changed the intraoperative procedure

and a total splenectomy would have to be performed. IPMNs and SCA have been described in co-occurrence with a variety of other pancreatic and non-pancreatic lesions however, the co-occurrence of SCA and IPMNs is a rarity. To our knowledge, only two other cases have been reported in the literature [25,26]. We are the first group to genomically analyse the two components separately using Next Generation Sequencing (NGS).

In contrast to IPMN, where studies have investigated the underlying genetic background, little is known about the exact pathogenic mechanisms underlying SCA and the co-occurrence of IPMN and SCA in particular [9]. One group suggested that the co-occurrence of IPMN with SCA could indicate a similar risk profile or molecular factors contributing to the development of these tumors [25]. Here, for the first time, we have sequenced these two co-occurring lesions separately using a next generation sequencing approach and did not identify any shared mutation. Our findings suggest that the IPMN and MSCA, at least in our patient, are not genetically related but rather present independent cystic neoplasias presenting as collision tumor.

Conclusion

Our report emphasizes the need for careful pre-therapeutic and intraoperative examination of cystic pancreatic lesions, ideally performed by experienced and diligent examiners and surgeons. In particular, we aim to highlight the fact that ambiguous cystic lesions of the pancreas may in fact represent synchronous (collision) tumors with significantly different malignant potential. We therefor strongly believe that all ambiguous (lesions with ambiguous pretherapeutic imaging results and/ or histology results) cystic lesions of the pancreas are best addressed using an interdisciplinary approach involving radiologists, surgeons and pathologists in order to ensure correct treatment choices.

Acknowledgement Authors Contribution

Ethics Approval and Consent to Participate

The study was conducted in accordance with the local ethical guidelines and approved by the local ethics committee under the number (13-091) of the University Hospital of Cologne, Germany. Written informed consent signed by the patient was obtained prior to the study.

Consent for Publication

The patient signed written informed consent for publication.

Availability of Data and Materials

Tissue blocks and stained sections as well as sequencing data are available upon request at the Department of Pathology of the University Hospital Cologne, Germany.

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Conflict of Interest

The authors declare no conflict interest.

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