



Case Report

Pancreatic Ductal Adenocarcinoma and “Pseudo-IPMN”

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Abstract

Cystic tumors of the pancreas bear the potential to be challenging entities for clinicians and pathologists. The most common cystic precursor lesion of pancreatic ductal adenocarcinoma (PDAC) is the intraductal papillary mucinous neoplasm (IPMN). As several cystic pancreatic lesions with distinct clinical consequences can be easily confused with IPMNs, awareness of morphological pitfalls to avoid misdiagnosis and mistreatment is important. Here we describe the clinicopathologic case of a 54-year-old male patient with a radiologically unexpected PDAC with large duct pattern/large duct type PDAC and address mimickers of IPMN (“pseudo-IPMN”).

Keywords: Large duct type PDAC; Large duct pattern; Pseudo-IPMN; Retention cyst; Intraductal spread; Cancerization

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most devastating cancers with a dismal prognosis, even after treatment by means of current modern multimodal medicine [1]. Mostly, PDAC presents as a solid tumor in association to macroscopically indiscernible precursor lesions, the pancreatic intraepithelial neoplasia (PanIN) [2]. However, in about 10%, PDAC is associated with macroscopic discernible cystic precursor lesions, especially intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN) [3]. Because cystic lesions of the pancreas other than IPMN can be easily misdiagnosed as IPMN clinically and pathologically, awareness of its common mimickers is necessary [4]. In this regard, the

term “pseudo-IPMN” refers to important differential diagnoses of cystic pancreatic lesions, such as duct ectasias/retention cysts, large duct type PDAC, simple mucinous cysts, pseudocysts, cystic tumor necrosis, groove pancreatitis-associated paraduodenal wall cysts and congenital cysts [3]. Here we report a case of a 54-year-old male patient, preoperatively presenting with a multicystic pancreatic lesion on radiologic imaging compatible with IPMN; pathological examination of the resection specimen revealed a large duct type PDAC with intraductal carcinoma spread into retention cysts of cancer-associated pancreatitis.

Clinical Presentation and Features

In June 2022, a 54-year-old male patient with a history of long-term smoking was referred to clinical attention due to loss of appetite without obvious reason and unprovoked weight loss of six kilograms within six months. Increased alcohol consumption and

permanent medication were negated; no other relevant secondary diagnoses were raised. A sonography of the abdomen, a computed tomography scan of chest, abdomen and pelvis, and a magnetic resonance cholangio-pancreaticography were performed, which showed a multilocular cystic lesion in the tail of the pancreas, measuring 67x38x60 mm, compatible with an IPMN or MCN. The diameter of the main pancreatic duct was normal in the proximal pancreas and increased abruptly in the transition to the tumor (9 mm). Thickened septa in the dorsal portion of the lesion but no enhancing nodules or lymphadenopathy were detected (Figures 1 and 2). Information on the cyst growth rate was not available, as prior imaging, studies were not performed. Analyses of cystic fluid was not performed as no cytological material was retrieved.

Serologically the tumour marker CA 19-9 was elevated at 81.9 kU/l (normal range < 37 kU/l). Suspicious liver lesions were excluded for malignancy with the magnetic resonance imaging including diffusion weighted imaging. After multidisciplinary tumor board discussion and pancreas specific consultation, a laparoscopic pancreatic left resection with splenectomy and lymphadenectomy was performed. The postoperative course was without major complications, a biochemical leak according to the ISGPS definition [5] was successfully treated with a drain. Because of the histological diagnosis of a PDAC, further therapy with adjuvant chemotherapy was recommended at the multidisciplinary tumor board and started five weeks after surgery.

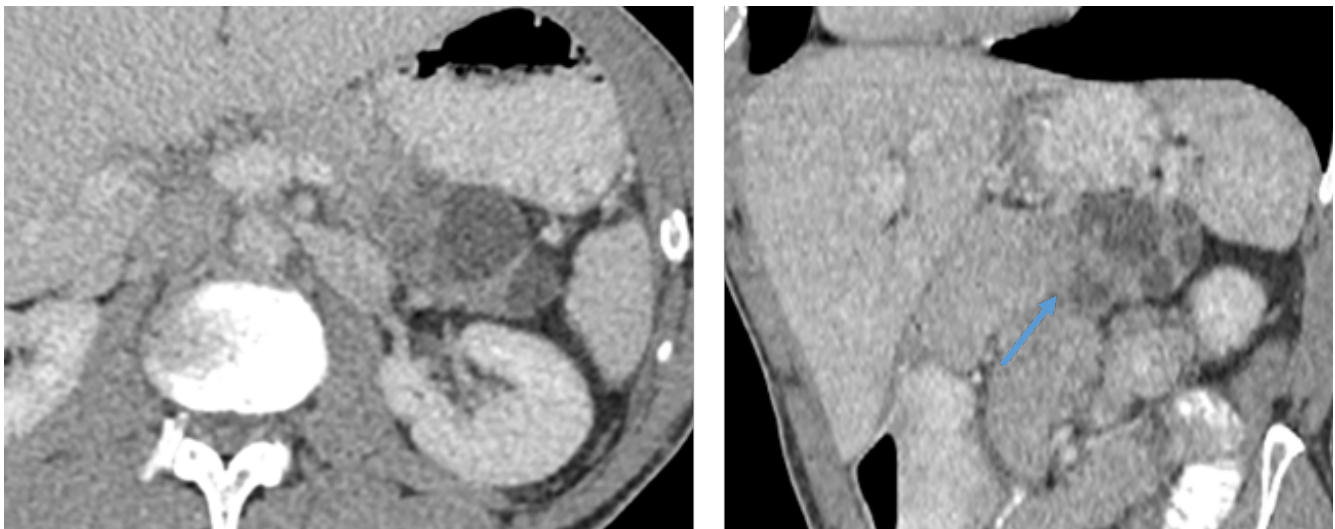


Figure 1: CT scan in portal venous phase in axial and coronal oblique plane demonstrating homogeneously hypodense corpus of the pancreas with non-dilated main pancreatic duct. In the pancreatic tail abrupt transition to a multilocular cystic mass with dilated main duct and total atrophy of the parenchyma distally of it. In the dorsal portion of the mass, there are thickened enhancing septa (arrow).

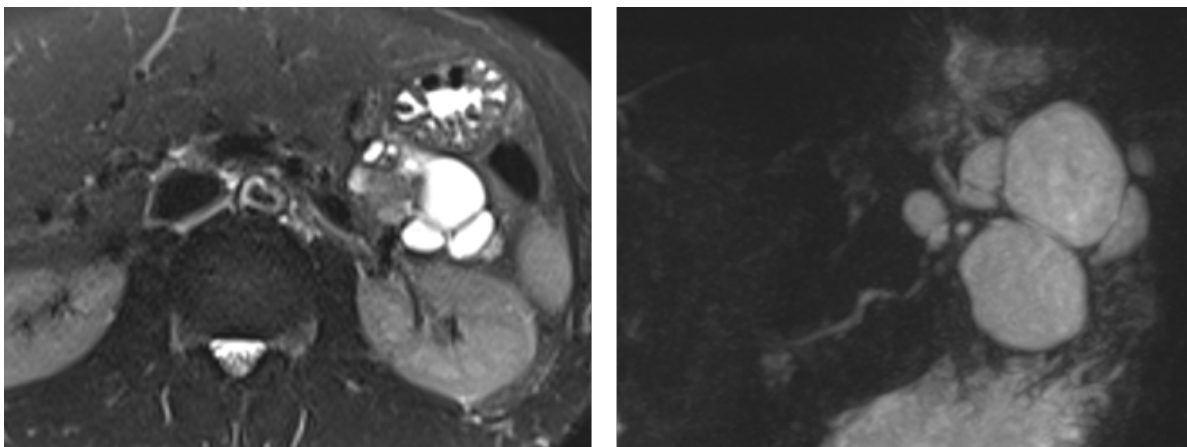


Figure 2: MRCP sequences a) 2D MRCP heavily T2 weighted axial images, b) MIP reconstruction of 3D MRCP images confirming CT findings.

Pathologic Presentation

A distal/left-sided pancreatectomy specimen with en-bloc splenectomy was received at the local Institute of Pathology. On perpendicular cut-sections to the main pancreatic duct, a solid tumor with microcysts and adjacent multilocular macrocysts was discovered (Figure 3). In detail, macroscopically the whitish solid tumor component measured 36x27x20 mm with microcysts covering about 60% of its cut surface, had a firm consistency and showed blurred, infiltrative borders; the adjacent multilocular cysts measured up to 28 mm, had a smooth contour and were filled with serous, non-mucinous fluid. A connection of the macrocysts to the pancreatic duct system was not detected and papillary fronds or tumor necrosis were absent. Microscopically (Figure 4) the solid tumor was mostly composed of irregularly configured and distributed expanded duct-like infiltrates. The lining was by mucinous, partly flattened and denuded, predominantly columnar cells with low to moderate cytological atypia, measuring more than 0.5mm and up to 8.6mm, corresponding to the large duct pattern of PDAC. A foamy, microvesicular appearing cytoplasm was detected in some glands. Glandular areas with distinct cell borders and an apical brush border-like band were also present. The nuclei were mostly well-polarized and basally located, sometimes pseudostratification was noted, intraluminal neutrophil granulocytes and granular debris was partly present in the expanded duct-like infiltrates. Papillary or cribriform areas and microcalcifications were not detected. Admixed and besides the dominant large duct-type component, usual PDAC not otherwise specified (NOS) with its typical small ducts and duct-like tumor cell compounds with variation in nuclear size was also present in about 40% of the tumor sections available. Up to eight tumor buds per 0.785mm² (intermediate budding, BD2) [6] and high-grade PanIN were recorded among the PDAC NOS component. Together with detection of perineural invasion and one per continuitatem lymph node metastases, a TNM stage of pT2 pN1 (1/50) L0 V0 Pn1 G2 R0 (according to UICC, 8th edition, 2017) was signed out. Of note, no lymph- or hemangiosis carcinomatosa was demonstrated. The carcinoma-associated stroma was overall desmoplastic in appearance with some more cellular areas. The adjacent macrocysts were located at the periphery of extensively atrophic and fibrotic pancreatic tissue in the setting of carcinoma-associated obstructive pancreatitis. Their arrangement was partly beads-on-a-chain-like, rimming the solid tumor component (Figure 5), reminiscent of a pattern similar to that of polycystic ovary, as described by Muraki et al [3]. The cyst epithelium presented partially denuded, partially as low cuboidal and columnar, duct-like with reactive atypia. However, repetitively abrupt transitions into foci of cancerization/intraductal spread by the adjacent PDAC, creating a PanIN-like appearance, were interspersed in these retention cysts and ectatic ducts. Some areas even offered a cribriform and irregular tufting morphology [7, 8]. Neither hematoxylin and eosin-stained tissue

slides nor immunohistochemistry for progesterone receptor showed ovarian-like stroma [9].



Figure 3: Macroscopic appearance of large duct type PDAC with microcystic areas and obstructive pancreatitis-induced retention cysts.

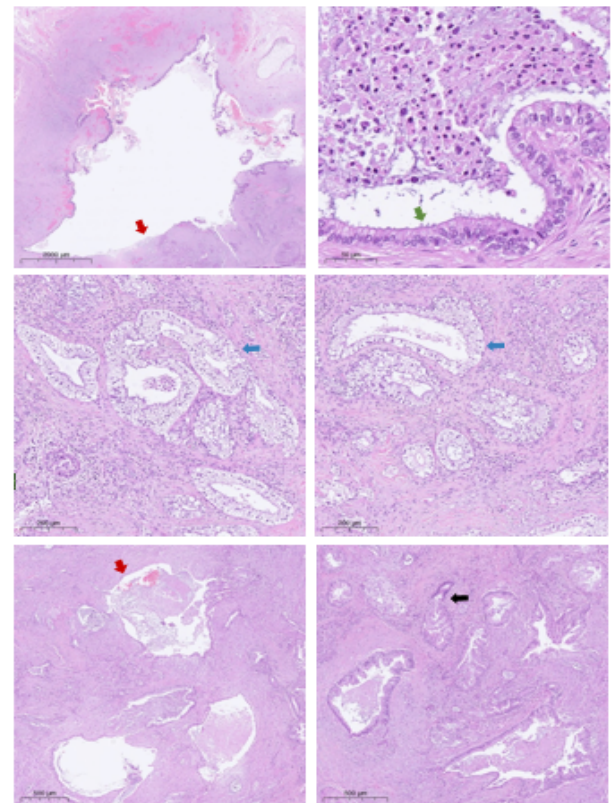


Figure 4: Atypical cyst-like expanded glands with partially attenuated, denuded lining (red arrows), apical brush border-like band sections (green arrow) and foamy cells (blue arrow) typical of large duct type PDAC; intraductal spread of PDAC/cancerization (black arrow).

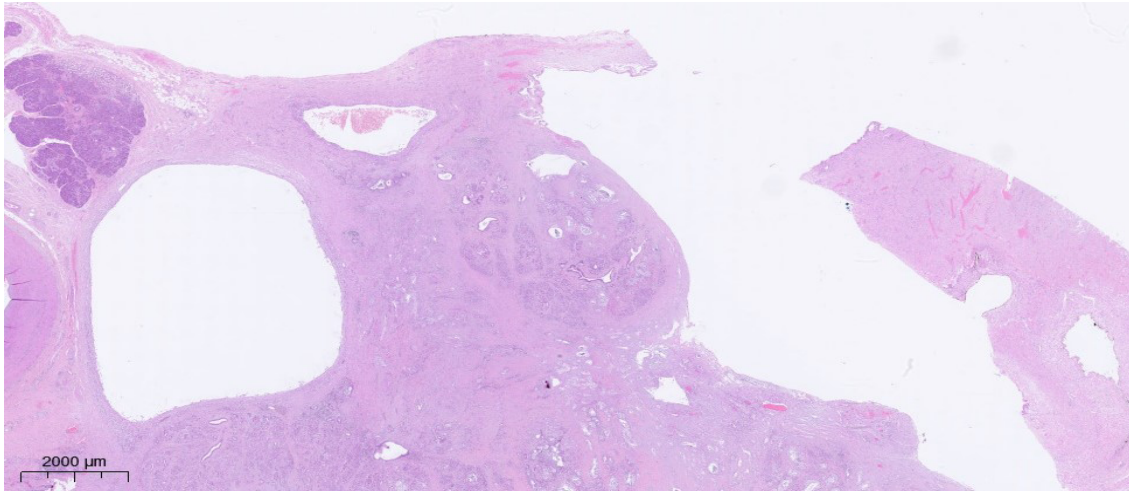


Figure 5: Overview of peripherally rimmed retention cysts and cancer-associated chronic pancreatitis; mid-lower area with PDAC NOS.

Discussion

The presented case of large duct type PDAC combined with cancerization of retention cysts and ectatic ducts of carcinoma-associated obstructive pancreatitis emphasizes the difficulties cystic pancreatic lesions can pose preoperatively for clinicians and postoperatively for pathologists. Especially confusion of non-malignant with malignant entities can put patients at risk of overtreatment or delayed adequate surgery and treatment [10]. In the majority of cases, PDAC appears radiologically and histologically as a solid tumor. However, cystic/pseudocystic lesions can overlay, accompany and mimic conventional PDAC NOS, hampering the correct diagnosis. Recently such lesions were summarized as “*pseudo-IPMN*” for their tendency to be easily confused with IPMN [3]. Among the denomination “*pseudo-IPMN*”, large duct type PDAC takes a special place. According to the 5th edition of the World health organization (WHO) Classification of Digestive System Tumors, large duct type PDAC qualifies as a growth pattern and not as a special type of PDAC (such as adenosquamous, micropapillary or anaplastic/sarcomatoid undifferentiated carcinoma, for instance). With over two decades of research concerning this pattern of PDAC, pathologic diagnostic criteria were specified and arguments in favor to categorize the large duct pattern of PDAC as a subtype of PDAC accumulated [3, 9, 11-15]. Irregular shaped, expanded ducts with a diameter of more than 0.5mm in the majority of the histological tumor sections (>50%), corresponding to macroscopic impression of microcysts and exclusion of mimickers set pathologists for the right diagnosis [9,12]. As in the presented case, a propensity for higher tumor size/T-stage, absence of lympho-vascular invasion, location in the body/tail part of the pancreas and better differentiation/grading are some clinic-pathological features attributed to large duct type PDAC as compared with usual PDAC NOS. Especially a recent

study reported better overall and progression-free survival for the large duct pattern of PDAC [13]. So far, systemic treatment recommendations do not differ between large duct pattern of PDAC and conventional PDAC. Interestingly, ROS1 mutations are more frequently observed in large duct type PDAC [7]. Current guidelines do not recommend routine next generation sequencing (NGS) testing in the adjuvant setting. However, preliminary data indicate that targeting ROS1 might be promising in metastatic PDAC as a further-line treatment option [16]. Another entity of the “*pseudo-IPMN basket*” is retention cysts/secondary duct ectasia, especially encountered in the setting of pancreatitis. As in the here presented case, large duct type PDAC with intraductal carcinoma spread into retention cysts of cancer-associated pancreatitis complicates a potentially already difficult radiologic and histologic diagnosis and emphasizes the importance to be aware of the “*pseudo-IPMN*” lesions, clinically and pathologically [3, 14, 15, 17, 18].

Conclusions

Cystic pancreatic lesions bear the potential to be challenging entities, radiologically and pathologically. Mimickers of IPMN (“*pseudo-IPMN*”) with different treatment implications exist. In this regard, awareness of diagnostic pitfalls like unexpected PDAC with large duct pattern/large duct type PDAC and intraductal cancer spread into retention cysts of carcinoma-induced pancreatitis is important.

Author Contributions: MW: conceptualization, original manuscript preparation (including pathologic diagnosis and images), discussion and review; NM/ASW: clinical presentation and features, manuscript preparation, discussion and review; VCO: radiological images and descriptions, manuscript preparation, discussion and review MB: manuscript preparation, discussion and review.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Statement of Ethics

Written consent on the publication of this case by the patient is present.

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