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The association of pancreatic cystosis and IPMN in cystic fibrosis: case report and literature review

D. PAGLIARI[1], A. SAVIANO[1], M.L. SERRICCHIO[1], A.A. DAL LAGO[1], M.G. BRIZI[2], R. MANFREDI[2], G. COSTAMAGNA[3], F. ATTILI[3]

[1]Department of Internal Medicine and Gastroenterology, Pancreatic Unit, Fondazione Policlinico Universitario "A. Gemelli", Catholic University of the Sacred Heart, School of Medicine, Rome, Italy
[2]Department of Radiology, Fondazione Policlinico Universitario "A. Gemelli", Catholic University of the Sacred Heart, School of Medicine, Rome, Italy
[3]Digestive Endoscopy Unit, Fondazione Policlinico Universitario "A. Gemelli", Catholic University of the Sacred Heart, School of Medicine, Rome, Italy

Abstract. – Pancreatic cystosis is a rare presentation of cystic fibrosis involving pancreatic gland. To date, only very few cases of pancreatic cystosis have been described in literature. Pancreatic cystosis may begin during the second decade of life and is the rarest presentation of cystic fibrosis. This disease is characterized by the presence of multiloculated cysts without ductal system communication of different sizes in all the pancreatic tissue. Herein, we report a case of a young woman affected by cystic fibrosis that was admitted to our Pancreatic Centre to evaluate a picture of diffuse multiloculated pancreatic cysts. After magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) assessment, we perform the diagnosis of the concomitant presence of the rare condition of pancreatic cystosis with Branch Duct-Intraductal Papillary Mucinous Neoplasm (BD-IPMN). To our knowledge, this is the first reported case of a cystic fibrosis patient with the combination of pancreatic cystosis and IPMN.

Key Words:
Pancreatic cystosis, Cystic fibrosis, Intraductal papillary mucinous neoplasm (IPMN), Pancreatic mucinous neoplasm, Magnetic resonance cholangio-pancreatography (MRCP).

Introduction

Pancreatic cystosis is a rare presentation of cystic fibrosis involving pancreatic gland[1]. It may usually begin during the second decade of life, but this condition may affect infants, children, and young adults with a history of cystic fibrosis. To date, only very few cases of pancreatic cystosis have been described in literature. Cystic fibrosis is an autosomal recessive disorder that is associated with systemic manifestations involving lungs and pancreas[2]. In particular, pancreatic gland in cystic fibrosis may be affected by different involvements, such as fibro-fatty replacement, atrophy, and pancreatic cystosis. In case of pancreatic cysts, several differential diagnoses are possible, such as pancreatic pseudocysts, intraductal papillary mucinous neoplasm of the pancreas (IPMN), serous and mucinous cystadenomas, von Hippel Lindau disease, polycystic kidney disease with pancreatic involvement, and hemorrhage cysts like lymphangioma. Commonly, in asymptomatic patients pancreatic cysts are an occasional finding of an abdominal ultrasound performed for general screening. Then, more specific diagnostic techniques are needed, such as magnetic resonance imaging (MRI), magnetic resonance cholangio-pancreatography (MRCP), and endoscopic ultrasound (EUS).

Clinical Presentation

A 46 years-old woman with a diagnosis of cystic fibrosis has been admitted to our Pancreatic Centre to evaluate the nature of different cysts located in the pancreas. The patient, with a positive family history for cystic fibrosis (mother and brother), was screened for 185 genetic mutations of CFTR gene. This genetic analysis revealed the presence of two CFTR gene mutations in heterozygosis as ΔF508 and 2789+5G>A. These latter are both described in literature as associated to a clinical phenotype of cystic fibrosis[2,3]. She received the first diagnosis of the pancreatic cysts by her General Practitioner with an occasional ab-

Corresponding Author: Danilo Pagliari, MD; danilo.pagliari@gmail.com

dominal ultrasound performed for general screening. The abdominal ultrasound reported multiple cystic lesions of different sizes in the head of the pancreas without other abnormalities of the pancreatic tissue. The patient was completely asymptomatic without episodes of acute pancreatitis, fever, malabsorption, and hyperglycemia history. She only reported constipation from her childhood. Her general blood exams revealed no anemia, no alterations of amylase, lipase, bilirubin, transaminase, coagulation tests, and oncologic markers (CEA, CA19.9). Oral glucose tolerance test (OGTT) was normal.

Imaging Findings

To better evaluate the pancreatic cysts, the patient did undergo EUS and MRI. These exams confirmed the presence of a major multiloculated cyst of 24 × 10 mm in the pancreatic head without signals of degeneration, and several little cysts in the pancreatic head/uncinate process. Six months later, the patient performed a EUS that showed a mild increase in the size (34 × 20 mm) of the major multiloculated cyst (Figure 1). Another follow-up after 6 months with abdominal MRI showed a further increase in the size of the major cyst (40 × 25 mm), with a multiloculated morphology and lined by true epithelium, and the presence of secondary cysts in the pancreatic head and body, the major of 15 mm in the head. Then, MRCP study revealed no communication between the major cyst and main pancreatic duct, while the secondary cysts resulted in communication with the ductal pancreatic system (Figure 2). After this MRI/MRCP, the patient received the diagnosis of Branch Duct-Intraductal Papillary Mucinous Neoplasm of the pancreas (BD-IPMN). Finally, EUS with fine needle aspiration (FNA-EUS) was performed and the analysis of the cystic fluid revealed a viscous content but amylase and

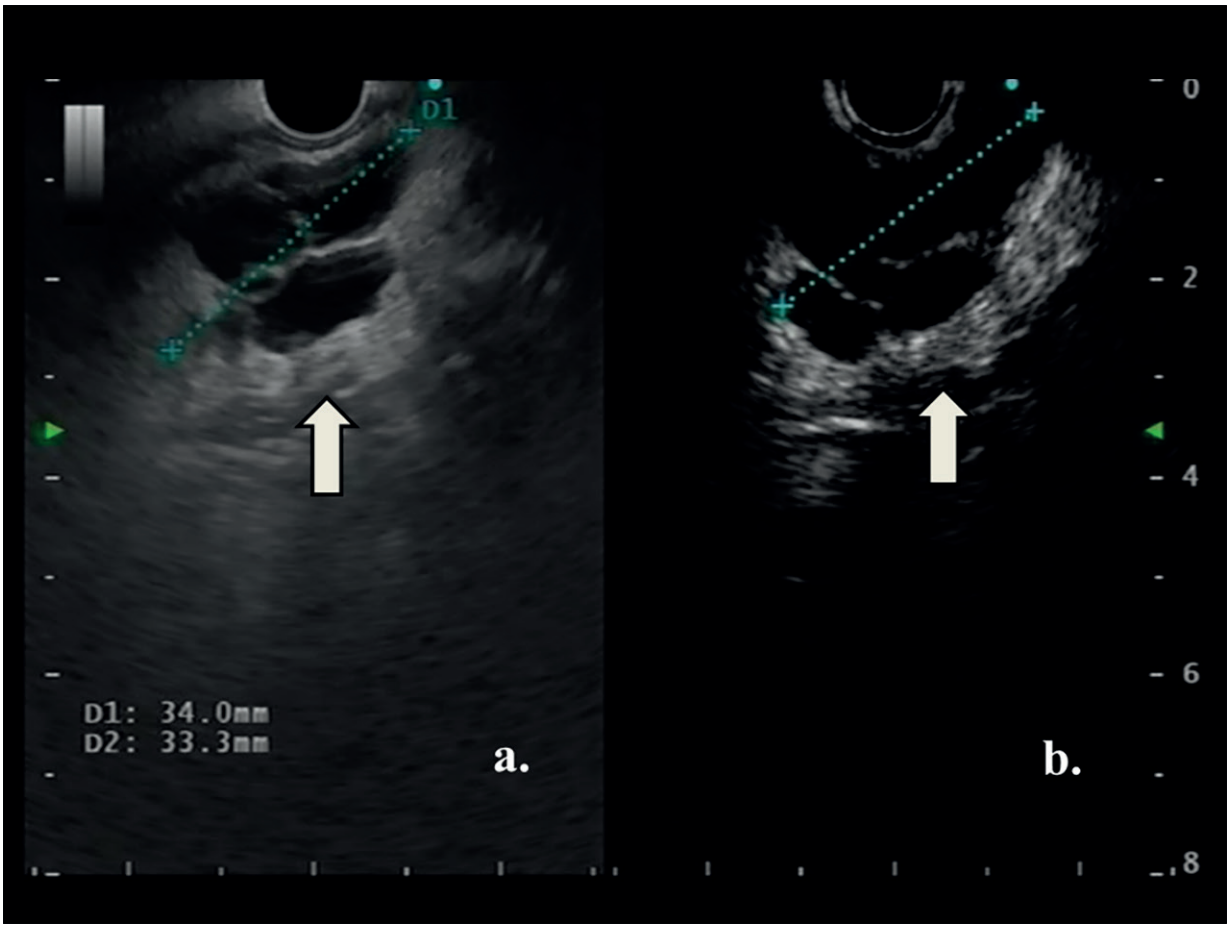

Figure 1. ***(a)*** Endoscopic ultrasound (EUS) showing a 34 mm multiloculated cyst of the pancreatic head constituted by several different cameras separated by thin septa. A hypoechoic tissue is present near the more posterior cyst (*arrow* in a). ***(b)*** After contrast-enhanced endoscopic ultrasound (CE-EUS), the hypoechoic tissue near the posterior cysts is not enhanced (*arrow* in b), and this finding confirms that it is a viscous content plug rather than a solid component.

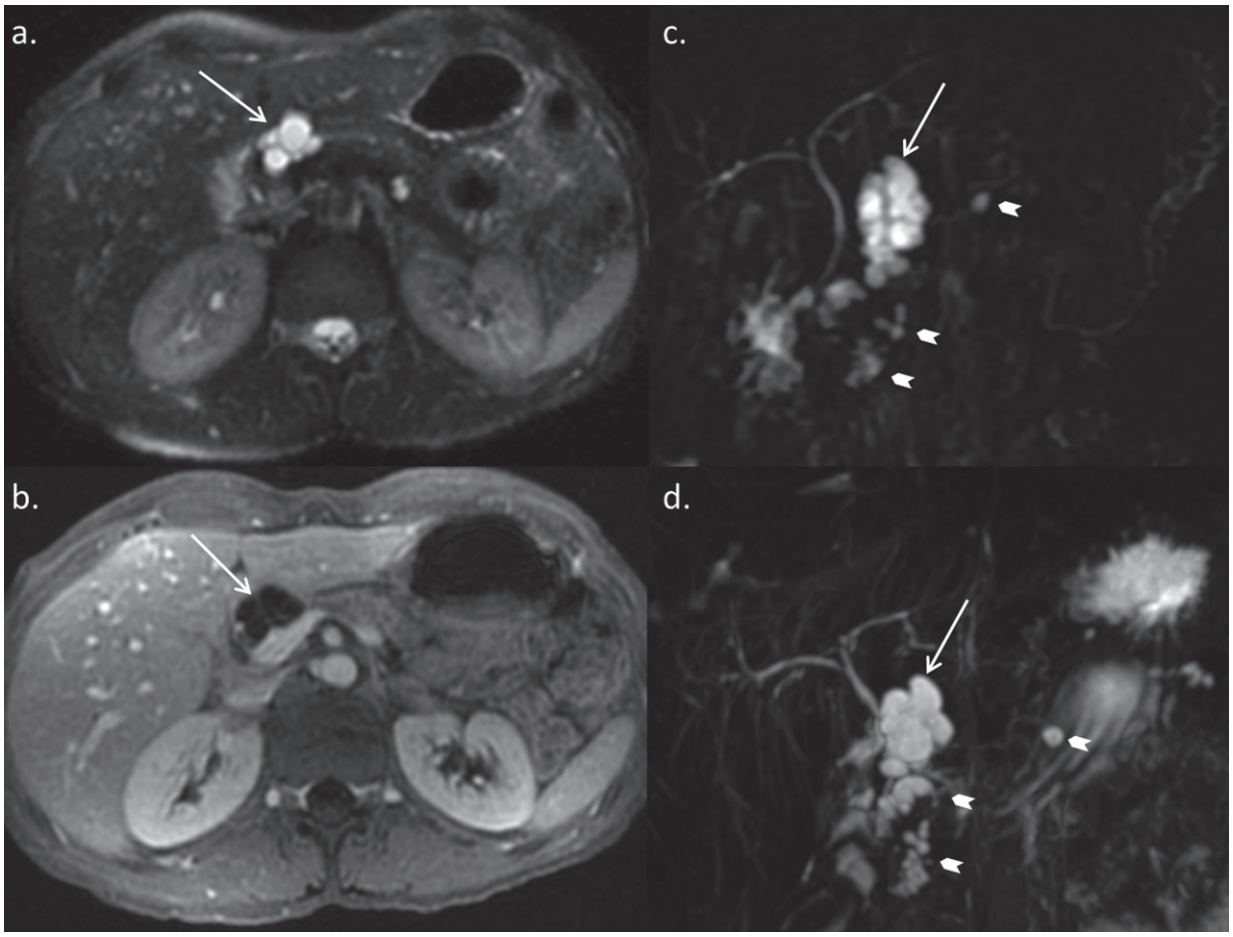

Figure 2. ***(a)*** Axial T2-weighted HASTE FS sequence shows a multilocular cystic lesion in the pancreatic head (*arrow* in a); axial T1-weighted FSPGR 3D LAVA post-contrast image ***(b)*** shows thin septations into the cyst without mural nodule; thick slab ***(c)*** and MIP multisection thin slab ***(d)*** FSE T2w MRCP confirm the major multiseptated cystic mass without any communication with the ductal pancreatic system (*arrow* in c, d) and show several little cysts in the pancreatic head and body in apparent communication with the main pancreatic duct (*arrowheads* in c-d).

CEA levels were undetectable due to the excessive viscosity of the pancreatic fluid. All these imaging findings combined with the clinical contest and patient's history suggested the diagnosis of pancreatic cystosis. Pancreatic cystosis is a rare condition associated with cystic fibrosis (regarding the multiloculated major cyst in pancreatic head/uncinate process), combined with the BD-IPMN (regarding the secondary cysts in pancreatic head and body).

Discussion

Pancreatic cystosis is a rare presentation of cystic fibrosis involving pancreatic gland. To date, only very few cases of pancreatic cystosis have been described in literature[1,4,5]. This condition may affect infants, children, and young adults with a history of cystic fibrosis. Cystic fibrosis is an autosomal recessive disorder that is usually associated with a systemic manifestation involving lungs and pancreas[6]. According to literature data, pancreatic gland in cystic fibrosis may be affected by 4 types of different involvements: (1) complete fibro-fatty replacement of the pancreatic gland (the most common, with an incidence of 42%); (2) atrophy without fibro-fatty replacement (with an incidence of 24%); (3) partial fibro-fatty replacement (most common in the pancreatic tail and associated with micro- or macro- cysts, with a prevalence of 16%); (4) pancreatic cystosis[7]. Pancreatic cystosis may begin during the second decade of life and it is the rarest presentation of cystic fibrosis. This disease is characterized by the presence

Table I. Differential diagnosis in pancreatic cysts considering epidemiological features, imaging, cysts features, evaluation, diagnosis and follow-up.

	Pancreatic cystosis	IPMN	Mucinous cystadenoma	Pancreatic pseudocyst	Pancreatic involvement in polycystic kidneys disease and Von Hippel-Lindau disease
Age	Child, young adult	Middle and older age	Middle age	All the age	Both in children and adults
Sex	No differences between sex are reported in literature	No differences between sex	Women	No differences between sex	No differences between sex
MRI	Hyperintensity in T2; Hypointensity in T1	Hyperintensity in T2; Hypointensity in T1	Hyperintensity in T2; Hypointensity in T1	Reveals pancreatic necrosis, fluid collections surrounded by a thin or thick wall, hyperintensity on T1-weighted	Hyperintensity in T2; Hypointensity in T1
EUS	Multiloculated cysts without communication with ductal system	Unilocular/ Multilocular cysts with communication with ductal system	Solitary uniloculated cyst without communication with ductal system	Uniloculated cyst without definite wall	Unilocular/Multilocular cysts diffused in all the pancreas
Number and size of cysts	Very numerous	Solitary/Multifocal cysts	Solitary cyst	Solitary cyst	Very numerous
Family history	Yes	Possible	Possible	No	Yes
Associated diseases	Cystic fibrosis	Genetic associated neoplasms	Genetic associated neoplasms	Inflammatory process or trauma	Kidney diseases
Communication with main pancreatic duct	Absent	Present	Absent	Absent/Present (in case of Wirsung rupture)	Absent
Main pancreatic duct	Dilated	Normal in BD-IPMN Dilated in MD/MT-IPMN	Normal	Normal	Multilocular cavities Acini intact
Other features	Epithelium-lined, thin, smooth and linear walls, absence of internal septa, mural nodules or signals of degeneration, and no enhanced	Possible presence of signals of degeneration (mural nodules, internal septa, enhanced walls)	Possible presence of signals of degeneration (mural nodules, internal septa, enhanced walls)	Completely fluid. Presence of necrotic or inflammatory stratified tissue in case of WON	Possible association with liver polycystic disease and cerebral aneurysms
Follow-up	Imaging	Imaging or surgical intervention	Surgical intervention	Imaging in case of asymptomatic patients/ EUS-guided or surgical- drainage in case of symptoms	Imaging if no symptoms, kidney/liver transplant in case of organ failure
EUS-FNA/ FNB	Not necessary	Useful for diagnosis and follow-up	Useful for diagnosis	Useful for diagnosis	Not necessary

Abbreviations: MRI, Magnetic Resonance Imaging; EUS, Endoscopic Ultrasound; IPMN, Intraductal Papillary Mucinous Neoplasm; BD, Branch Duct; MD, Main Duct; MT, Mixed Type; WON, Walled-Off Necrosis.

of multiloculated cysts of different sizes in all the pancreatic tissue[1,4], so that, in the most advanced cases, the recognition of the normal pancreatic tissue become highly difficult. Different combined imaging techniques are useful to better evaluate this condition. In MRI, cysts show high and bright signal intensity on T2-weighted images and low signal on T1-weighted images due to the high protein content and the low water content in pancreatic secretions and defect in bicarbonate transport. Usually, cysts are lined by true epithelium and present thin, smooth and linear walls, absence of internal septa, mural nodules or signals of degeneration, and no enhancement after intravenous injection of contrast material[8,9]. EUS-FNA may reveal the cystic fluid as of serous type, with amylase and protein levels similar to the serum ones[10]. Importantly, different from IPMN, cysts in pancreatic cystosis don't have communication with the ductal system. The range of macroscopic cysts is from 15 to 120 mm[11]. They can produce inflammatory reactions, progressive fibrosis, calcification and atrophy of pancreatic tissue[12]. Commonly, pancreatic cystosis patients are asymptomatic or they can suffer from non-specific abdominal pain due to the mass effect or hemorrhage into the cysts of major size[13-15]. Large cysts may cause the displacement of the spleno-portal venous and arteriosus structures, such as the portal vein and superior mesenteric artery[9]. The enlargement of the cysts may also cause main and secondary pancreatic ducts obstructions, due to the accumulation of abnormal and viscous fluid. This condition is related to an exocrine pancreas replaced by fatty tissue that causes exocrine insufficiency[8]. Indeed, pancreatic cystosis may be suspected in the clinical context of patients with cystic fibrosis and multiloculated diffused pancreatic cysts. Then, MRCP may reveal the absence of communication with pancreatic ductal system, and EUS-FNA may reveal the viscous content of the cysts, that results as serous type after biochemical analysis[16]. Biopsy is considered unnecessary for the diagnosis of pancreatic cystosis[17]. Several differential diagnoses of pancreatic cysts has to be considered, such as pancreatic pseudocysts, IPMN, serous and mucinous cystadenomas, von Hippel Lindau disease, polycystic kidney disease with pancreatic involvement, and hemorrhage cysts like lymphangioma. In case of pancreatic pseudocysts[18], the patient should have a history of inflammation or trauma (Table I). IPMN shows communication with pancreatic ductal system and cysts are more numerous and little in size than macrocysts of pancreatic cystosis. Mucinous cystadenomas are commonly diagnosed in middle-age woman and EUS-FNA reveals mucinous content. Polycystic and von Hippel Lindau disease may be excluded if kidney appears normal. Finally, lymphangioma shows a haemorrhagic cystic content in MRI, that results different from viscous secretion of cystic fibrosis. Thus, the clinical contest can help with the diagnosis[19] The overall risk of cancer incidence in patients with cystic fibrosis is similar to general population, while the risk of gastrointestinal tract and pancreatic neoplasms appear to be increased[8,18]. To date, literature data revealed that no malignant transformation of pancreatic cystosis has been reported[4,8,18]. However, few cases of mucinous cystadenomas in cystic fibrosis patients with pancreatic cysts have been described[10].

Conclusions

The management of this condition includes follow-up with MRI in symptomatic patients and abdominal ultrasound in asymptomatic patients. In general, surgical intervention should be avoided, but it should be considered in patients with abdominal discomforts, persistent gastrointestinal symptoms, increased volume of the macrocysts, in order to avoid the malignant transformation of the possible concomitant mucinous neoplasms[8,11,18]. The peculiarity of our case is the combination of pancreatic cystosis and IPMN.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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