

## Contemporary Challenges in the Clinical Management of Pancreatic Cystosis

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Pancreatic cystosis is an exceedingly rare condition in which the pancreatic tissue is replaced by multiple cystic structures throughout the pancreas, prevalent in patients suffering from cystic fibrosis (CF). CF is a life threatening, autosomal recessive, inherited disease, most commonly caused by deletion of residue 508 in the CF trans-membrane regulator gene (CFTR) [1,2]. This defective CFTR gene causes abnormal chloride transport across the membrane of epithelial cells. Impaired epithelial trans-membrane ion transport results in abnormally thick secretions, which negatively affect the lungs, pancreas, para-nasal sinuses, liver, and reproductive tract. Patients with CF display a wide array of pathologies, which are dependent on the efficacy of chloride ion conduction through the CFTR [3].

CF patients present a change throughout the body in the nature of mucous and serous secretions so that the mucous secretions are particularly dry while the serous are abnormally concentrated. The lung is the primary organ affected by CF, however 90% of patients will show pancreatic involvement. Long-term pancreatic obstruction causes dilation of the ducts and loss of pancreatic tissue, which is replaced by fibrous tissue. This leads to the loss of exocrine and endocrine pancreatic function, 90% of pancreatic tissue is to be lost before symptoms such as steatorrhea, fat intolerance, abdominal pain, and diabetes appear.

According to the CF foundation patient registry annual report, the predicted survival of CF patients has increased from 26 years in the early 90s to more than 38 years of age in 2010 [5]. The improvement in CF treatment causes most likely an increase in predicted survival, but on the other hand long survivors of CF are facing meaningful complications of an already complex pancreatic disease such as pancreatic cystosis. It seems appropriate than to discuss the long-term management and challenges in patients suffering from this disease.

Pancreatic complications of CF include exocrine and endocrine pancreatic insufficiency, pancreatitis, pancreatic cystosis and pancreatic cancer. Both exocrine and endocrine insufficiencies are readily treatable with replacement therapy. A recent survey, showed that 0.5% of the patients with CF will develop chronic pancreatitis [6], significantly higher than the general population (0.01-0.02%). Long survivors of CF have higher risk of developing chronic pancreatitis and in fact 45% of the patients that developed pancreatitis were above

35 years of age [7]. The risk and complications of chronic pancreatitis seems more relevant knowing the increased risk for pancreatic cancer in that specific cohort. Sheldon et al. [8] described 0.5% incidence of pancreatic cancer in a cohort of 412 patients with CF. Neglia et al. [9] described increased incidence of digestive tract cancer in CF patients and incidence of pancreatic cancer of 0.01% in a cohort of 38,000 patients.

Imaging of the pancreas throughout the life of a CF patient may display different pancreatic tissue changes. Changes include partial replacement of the pancreas by fibro-fatty tissue (16%) that may lead to a complete fibro-fatty replacement (42%) or atrophy of the pancreas (24%). All three types of changes may be accompanied by the presence of micro or macro-cysts [10].

Pancreatic cystosis (PC) has been reported anecdotally in the literature [10-15]. In PC the pancreatic parenchyma is replaced with multiple cysts of different sizes throughout the pancreas. Hernanz-Schulman et al. [11] reported that fluid content of the cysts is mainly serous with amylase and protein levels being equivalent to that of serum. Microscopic evaluation of the cysts revealed one layer of epithelium with occasional hyperplastic foci, with piling up of the epithelium to several layers.

In a CF patient with pancreatic cystic disease the differential diagnosis should include also other cystic pathologies of the pancreas such as: pseudocysts, polycystic disease, pancreatic involvement of Von-Hippel Lindau disease, Lymphangiomas, Pancreatic micro and macro-cystic adenomas, serous and mucinous cyst adenomas, intraductal papillary mucinous neoplasms and more importantly the malignant degeneration of such lesions.

So far there are no reports of malignant transformation within pancreatic cystosis but there are reports of development of mucinous adenomas in pancreatic cysts in CF patients [10]. Presently we are taking part in the care of a 17 year old female that was referred to the emergency room (ER) due to continues abdominal discomfort and palpable epigastric mass. A computerized tomography revealed multiple cystic structures replacing the pancreatic parenchyma, of which one abnormally large compressing the surrounding tissues, the diagnosis of pancreatic cystosis was performed. The functional status of the patient was exceptional and percutaneous aspiration of

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that symptomatic large cyst was opted. Drainage provoked immediate relief of her symptoms, fluid was mucinous, with normal amylase levels and carcino embryonic antigen (CEA) levels from the fluid in the cyst came back 310 ng/mL. Although no reports are available of malignant transformation within PC so far, but does one should ignore such a significant finding?

What should be than the correct management of a patient with pancreatic cystosis? In recent years the surgical approach for pancreatic cystic disease has changed vastly towards a more aggressive approach taking into consideration that although, serous cysts tends to be benign, up to 40% of the mucin-producing neoplasms are malignant. Therefore the corner stone of a pancreatic cystic lesion evaluation is the determination whether a lesion is mucin producing or not, which might be difficult to determine. Computed tomography (CT) although the gold standard for the diagnosis of pancreatic lesions has shown to have ability as low as 23-41% in differentiating serous and mucin producing lesions [18], endoscopic ultrasound (EUS) did not yield better results [19].

The cooperative pancreatic cyst study showed that the most accurate way to determine whether a lesion is mucin-producing or not is by determining the levels of carcinoembryonic antigen (CEA) within the fluid of the cyst. Levels higher than 192ng/mL are associated with mucin producing lesions; levels above 300ng/mL are associated with malignant degeneration. This method had a sensitivity of 75%, specificity of 84% and diagnostic accuracy of 79% [20]. DNA mutational analysis of the fluid in the cyst showing high levels of K-ras-2 and loss of heterozygosity may be associated with mucin producing lesions, but CEA levels were found to be more specific [21]. The serum levels of cancer antigen 19-9 (CA 19-9) is a good adjunct to diagnosis, and have been reported previously to be elevated in the presence of malignant degeneration and development of invasive cancer in patients with pancreatic cystic disease [22].

The diagnosis is often made easy when only one lesion is present, as needle aspiration of the cyst either percutaneously or more commonly by endoscopic ultrasound can provide fluid samples. However, when the entire pancreas is replaced by dozens of cysts there is no accurate way to sample them all. Therefore, should a total pancreatectomy be performed? [1,12,13] If not, should the patient than be left untouched despite symptoms, and increased risk of developing pancreatic malignancy? [1,14] Or only drained for symptoms relief? [15]. This is a somewhat complicated question, and at this time there is no evidence-base available to answer that question. The surgical approach should be balanced by, the possibility of pancreatic cancer development, the limited survival of CF patients and the functional status of the patient.

Surgical options are varied and include; drainage for large symptomatic cysts, by endoscopic or open gastro or duodeno-cystostomy, percutaneous drainage or aspiration, and partial or total pancreatectomy.

The first thing to consider in the clinical management of a patient with PC, is the chronological age of the patient at the time of diagnosis, as a 9 year old diagnosed with PC is not deemed for the same treatment of a 38 years old with the same diagnosis. Alongside with the chronological age, the functional status of the patient is of utmost importance, as a patient with a chronically reduced FEV1 and recurrent respiratory exacerbations is at increased risk for postoperative complications.

A symptomatic patient with no doubt needs remedy for his symptoms, if it is by drainage of a large anterior cyst that compresses

the stomach, causing early satiety nausea, or even recurrent vomiting or a large posterior cyst that causes pain. Once drainage or aspiration is performed the quality of the fluid must be thoroughly examined for amylase, proteins, CEA levels and serum CA19-9.

If the levels of CEA are abnormal then surgery should be offered if the patient's functional status permits it. In patients with serous fluid in the cyst, with normal amylase, protein and CEA levels in cyst fluid, we cannot exclude that other cysts that were not sampled are not to have abnormal levels. In this case, if the patient's functional status permits, all options should be offered to the patient and both patient and surgeon should reach an educated decision considering all pros and cons of the different possibilities. While considering the various options the patient should be aware of the fact that there is no good way to follow such numerous lesions and risks of pancreatic cancer development along with the risks of surgery should be clarified.

In conclusion although pancreatic cystosis is seemingly rare, the challenges in clinical management of such pathology are imminent. The development of pancreatic cancer within those cysts is more than relevant facing a disease with improved treatments and therefore improved survival. The clinician should base his decisions on the age of the patient at presentation, functional status and the presence of symptoms alongside with levels of CEA in the cyst fluid and CA19-9 in the serum.

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