Pancreatology xxx (2018) 1–5

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Pancreatic cystosis in patients with cystic fibrosis: A qualitative systematic review

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ARTICLE INFO

Article history:
Received 24 April 2018
Received in revised form
29 July 2018
Accepted 16 August 2018
Available online xxx

Keywords:
Pancreas
Cysts
Pancreatectomy
Cystic fibrosis
Chronic pancreatitis

ABSTRACT

Background: Patients with cystic fibrosis (CF) and a CFTR gene mutation may present with a variety of pancreatic disorders. The presence of multiple macrocysts (>1 cm) replacing the entire pancreatic parenchyma is termed pancreatic cystosis. Lack of clear data makes clinical decision making challenging and controversial. The aim of this review is to perform a qualitative systematic analysis of the literature with intention to evaluate management plans.

Methods: Electronic databases MEDLINE, Embase, and Scopus were searched for relevant studies, and 19 studies describing patients with pancreatic cystosis were included and analyzed for clinical features and therapy offered.

Results: The data of 24 patients were collected from included studies. Eight cases (33%) had a documented CFTR gene mutation and 10 (42%) were symptomatic at presentation. Imaging modalities included ultrasound in 18 (75%), CT in 12 (50%), and MRI in 8 (33%) cases. An average size of the largest cyst was 5.4 cm. 6 (25%) patients were offered therapy that described surgical (3), endoscopic (1), or medical therapy (2). Surgeries offered included total pancreatectomy, partial pancreatic resection of uncertain extent, and complex cyst resection. Endoscopic treatment was cystogastrostomy. Novel medical treatment was utilized with Doxepin, Propantheline, and Clonidine, resulting in reduction in cyst size and overall clinical improvement.

Conclusion: Patients with pancreatic cystosis should not be denied treatment when necessary. This literature review is the most comprehensive thus far of cystic fibrosis and pancreatic cystosis, and it did not provide identification of a definitive treatment plan or demonstrate contraindication to specific therapies.

1. Introduction

Patients with cystic fibrosis (CF) have many extra-pulmonary disease manifestations, the most notable of which are gastrointestinal and include the pancreas [1]. Pancreatic disorders associated with the CFTR gene mutation include acute pancreatitis, acute on chronic pancreatitis, exocrine pancreatic insufficiency, and/or pancreatic cyst formation [2]. Certain CFTR gene mutations are also responsible for an increased risk of developing pancreatic cancer [3]. Radiologically, the pancreas of a patient with CF may vary in appearance, ranging from a normal pancreas, partial or complete lipomatous change, microcystic or macrocystic appearance, or an atrophic pancreas [4]. Patients with multiple pancreatic cysts can have microcysts, which are defined as measuring <1 cm in size, or they can have macrocysts, which are defined as cysts >1 cm in size. The presence of multiple macrocysts is termed pancreatic cystosis [5–7]. Patients with pancreatic cystosis often have exocrine insufficiency and variable endocrine function. Their clinical presentation varies, as some patients may be completely asymptomatic, whereas cystosis is found in some patients with gastrointestinal symptoms such as abdominal pain, nausea, fullness, and poor quality of life.

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https://doi.org/10.1016/j.pan.2018.08.008
1424-3903/

As this diagnosis is rare in overall incidence, with scant data to guide management, it is difficult for physicians who provide care for patients with pancreatic cystosis. The absence of clinical guidelines may compel physicians to take a non-interventional approach until proven treatments are established [8]. However, it will be difficult to find an appropriately large population of these patients to allow for development of a prospective, research-based treatment algorithm. In a recent review of pancreatic involvement in CF patients, Freeman et al. suggested a theoretical decision-making algorithm including surgical and endoscopic management [2].

The aim of this review is to perform a qualitative systematic analysis of the literature regarding pancreatic cystosis in patients with cystic fibrosis. The intention is to evaluate management plans that have been utilized for this condition.

2. Methods

We employed a medical librarian to develop search strategies for the concepts of cystic fibrosis and pancreatic cystosis. These strategies were created using a combination of subject headings and keywords used to search MEDLINE via PubMed, Embase, and Scopus, from the date of database inception to November 28, 2017. Database-supplied limits for English language and journal article publication types were used. The searches in MEDLINE, Embase, and Scopus yielded a total of 757 citations. These results were exported to Endnote Desktop, and 335 duplicates were removed using the Endnote deduplication feature. This resulted in a total of 422 unique citations. The complete strategies for each of these searches can be found in Table 1. Two additional articles were identified by backhand searches. These citations were imported into the review software Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Two authors performed title and abstract screening, and all irrelevant articles were omitted. Of the remaining articles, a full text screening was performed, and articles describing pancreatic cystosis were selected. Articles were excluded under three headings: 1) wrong patient population, 2) articles of patients with CF and pancreatic disease that do not specifically address cystosis, and 3) letters/commentary/radiological review describing the same patients whose primary articles were included. Included articles were evaluated for the patients' demographics, presentation, comorbidities, clinical and radiological findings, treatment provided, and outcomes.

3. Results

3.1. Literature search

Out of 424 unique citations, 42 articles were selected by title and abstract screening. In review of those 42 articles, 19 were identified that described patients with pancreatic cystosis and were used for data collection. Of the remaining publications, 12 were excluded for identifying the wrong patient population, 6 due to the identified patient population not pertaining to the pathology in evaluation, and 5 for redundant review of patients described in the included papers (Fig. 1).

3.2. Patient cohort

A total of 24 cases were described in the 19 publications. Of those cases, 15 (63%) patients were female and 9 (37%) patients were male. The average age was 15 years (range 2–44). The average age at diagnosis of cystic fibrosis was approximately 3 years. Weight and height were infrequently included, but of the 2 case reports (8%) including those metrics, the average BMI was 15 (22 cases (92%) did not describe height and weight together) [9,10]. The range of follow-up from the year of diagnosis of pancreatic cystosis to the time of publishing was <1–16 years, with an average of 6 years. Diabetes mellitus was described in only 2 case reports (8%) [11,12]. The medication regimen and/or insulin requirement for these cases was not described. Eight case reports (33%) included documentation of a known CFTR gene mutation [4,7,9,12–15], and 6 of 8 (75%) described mutations were homozygous delta f508[4,7,9,12–14]. The remaining case reports (67%) did not describe a genetic mutation. Pancreatic insufficiency requiring enzyme replacement was described in 10 cases (42%), and in 3 of those 10 cases CFTR gene mutation was concurrently described. Eleven cases (46%) had documented comorbidities, which included pulmonary infections and/or recurrent upper respiratory infections [9,15–18], cor pulmonale [19], and pulmonary colonization [9]. Antibiotic regimens were infrequently described in these case reports (only 1 of 24 cases or 4%) [10]. Symptoms were noted in ten cases (42%) at presentation [6,7,11,12,15–18,20,21]; five cases (21%) were

Table 1
The Search Strategy utilized to identify unique citations for review.

Database	Search Strategy Run 11/28/2017	Number of Studies Found	After Duplicate Removal
MEDLINE (via PubMed)	(((((("Pancreatic Cyst" [Mesh] OR pancreatic cystosis [tw] OR pancreatic cystadenoma [tw] OR pancreatic cystadenomas [tw] OR pancreas cyst [tw] OR pancreas cysts [tw] OR pancreatic cyst [tw] OR pancreatic cysts [tw] OR pancreatic cystic [tw] OR pancreatic macrocyst [tw] OR pancreatic macrocysts [tw] OR pancreatic macrocystosis [tw] OR pancreatic cystadenocarcinoma [tw] OR pancreatic cystadenocarcinomas [tw]))) OR (("Pancreatitis" [Mesh] OR pancreatitis [tw]) AND (cyst [tw] OR cysts [tw])))) AND (("Cystic Fibrosis" [Mesh] OR cystic fibrosis [tw])) AND English [Language]	225	135
Embase	('pancreas cyst'/exp OR 'pancreatic cystosis' OR 'pancreatic cystadenoma' OR 'pancreatic cystadenomas' OR 'pancreas cyst' OR 'pancreas cysts' OR 'pancreatic cyst' OR 'pancreatic cysts' OR 'pancreatic cystic' OR 'pancreatic macrocyst' OR 'pancreatic macrocysts' OR 'pancreatic macrocystosis' OR 'pancreatic cystadenocarcinoma' OR 'pancreatic cystadenocarcinomas' OR (('pancreatitis'/exp OR pancreatitis) AND (cyst OR cysts))) AND ('cystic fibrosis'/exp OR 'cystic fibrosis') AND ([article]/lim OR [article in press]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [review]/lim) AND [english]/lim AND [embase]/lim	201	99
Scopus	((pancreatitis AND (cyst OR cysts)) OR ("pancreas cyst" OR "pancreatic cystosis" OR "pancreatic cystadenoma" OR "pancreatic cystadenomas" OR "pancreas cysts" OR "pancreatic cyst" OR "pancreatic cysts" OR "pancreatic cystic" OR "pancreatic macrocyst" OR "pancreatic macrocysts") OR ("pancreatic macrocystosis" OR "pancreatic cystadenocarcinoma" OR "pancreatic cystadenocarcinomas")) AND ("cystic fibrosis") AND (LIMIT-TO (DOCTYPE,"ar") OR LIMIT-TO (DOCTYPE,"re") OR LIMIT-TO (DOCTYPE,"ed") OR LIMIT-TO (DOCTYPE,"le")) AND (LIMIT-TO (LANGUAGE,"English"))	331	188
Total		757	422

Please cite this article in press as: Desai CS, et al., Pancreatic cystosis in patients with cystic fibrosis: A qualitative systematic review, Pancreatology (2018), https://doi.org/10.1016/j.pan.2018.08.008