

Follow-up of patients with pseudotumoral chronic pancreatitis: Outcome and surveillance

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Abstract

AIM: To follow up patients with pseudotumoral chronic pancreatitis (PCP) to assess their outcome and identify an optimal surveillance interval.

METHODS: Data obtained prospectively were analyzed in a retrospective manner. Patients with clinical evidence of chronic pancreatitis (abdominal pain in

the epigastrium, steatorrhea, and diabetes mellitus), endoscopic ultrasound (EUS) criteria > 4, and EUS-fine needle aspiration (FNA) were included. A pseudotumor was defined as a non-neoplastic space-occupying lesion, a cause of chronic pancreatitis that may mimic changes typical of pancreatic cancer on CT or endoscopic ultrasound but without histological evidence. A real tumor was defined as a neoplastic space-occupying lesion because of pancreatic cancer confirmed by histology.

RESULTS: Thirty-five patients with chronic pancreatitis were included, 26 (74.2%) of whom were men. Nine (25.7%) patients were diagnosed with pseudotumoral chronic pancreatitis and two (2/35; 5.7%) patients with pseudotumoral chronic pancreatitis were diagnosed with pancreatic cancer on follow-up. The time between the diagnosis of pseudotumoral chronic pancreatitis and pancreatic adenocarcinoma was 35 and 30 d in the two patients. Definitive diagnosis of pancreatic adenocarcinoma was made by surgery. In the remaining six patients with pseudotumoral chronic pancreatitis, the median of follow-up was 11 mo (range 1-22 mo) and they showed no evidence of malignancy on surveillance. In the follow-up of patients without pseudotumoral chronic pancreatitis but with chronic pancreatitis, none were diagnosed with pancreatic cancer. According to our data, older patients with chronic pancreatitis are at risk of pseudotumoral chronic pancreatitis.

CONCLUSION: According to characteristics of patient, detection of PCP should lead a surveillance program for pancreatic cancer with EUS-FNA in < 1 mo or directly to surgical resection.

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Key words: Chronic pancreatitis; Pseudotumoral chronic pancreatitis; Surveillance; Endoscopic ultrasound

Core tip: Actually, there are no clear recommendations for follow-up of patients with chronic pancreatitis and solid pancreatic mass lesions. We followed-up patients with chronic pancreatitis and solid pancreatic mass lesions and we assessed the final outcome and identified an optimal surveillance interval. We found that almost one-third of patients with chronic pancreatitis had pseudotumoral chronic pancreatitis, and 22.2% had unresectable pancreatic adenocarcinoma less than 2 mo after the initial diagnosis. Endoscopic ultrasound fine needle aspiration can miss malignancy in nearly 25% of patients with pseudotumoral chronic pancreatitis.

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INTRODUCTION

Pancreatic cancer (PC) at diagnosis is unresectable in 70% of cases^[1]. The risk of developing PC is increased in patients with chronic pancreatitis. Surveillance in patients with chronic pancreatitis may represent an opportunity for early detection of PC^[2]. The increase in risk for PC in patients with chronic pancreatitis ranges from 14.4-26.7 times in 10-year follow-up^[1,3]. It is difficult to differentiate by images between pancreatic carcinoma and pseudotumor in the context of chronic pancreatitis^[4,5]. In case of endoscopic ultrasound (EUS) some criteria have been proposed, but even using the fine needle aspiration (FNA) biopsy, the results have not been satisfactory^[6,7]. Actually, there are no clear recommendations for follow-up of patients with chronic pancreatitis and solid pancreatic mass lesions^[8]. The aim of this study was to follow up patients with chronic pancreatitis and solid pancreatic mass lesions to assess the final outcome and identify an optimal surveillance interval.

MATERIALS AND METHODS

Data obtained prospectively were analyzed in a retrospective manner. Electronic and paper records of consecutive patients evaluated from March 2005 to December 2012 were evaluated. Patients with clinical evidence of chronic pancreatitis, EUS criteria > 4, and EUS FNA were included^[9]. According to the local Ethics Committee, all patients signed an informed consent document.

Before the procedure, all patients had laboratory tests including prothrombin time and full blood count. The patients were placed in a left decubitus position and sedated using a combination of midazolam, propofol, and fentanyl by an anesthetist. Patients were continually monitored with an automated noninvasive blood

pressure device, electrocardiogram, and pulse oximetry throughout the procedure. EUS was performed with a linear array echoendoscope, GFUCT-140 (Olympus America Inc; Center Valley, PA), by two echoendoscopists. All patients were hospitalized, and after the procedure they were observed with an automatic monitor for at least 4 h for surveillance of possible complications.

EUS FNA (standard needle)

At first, the transducer was brought into a stable position in front of the targeted lesion. The metal spiral was then introduced into the biopsy channel, observing carefully that the needle piston was securely locked and the needle was completely retracted. The spiral was inserted entirely and the handle with the Luer-lock firmly screwed onto the biopsy channel. To ensure that the sheath was protecting the entire length of the working channel, we used the optic of the endoscope. With the stylet retracted but still inside the needle, the biopsy needle was moved forward into the lesion under full real-time ultrasound control. After penetration into the middle of a lesion, the stylet was completely removed. Upon reaching the optimal needle position in the middle of the lesion, a 10 mL syringe with a locking device was firmly screwed on the needle, and the syringe piston was pulled to create a low pressure. The syringe piston was locked in this position for permanent suction. The needle was moved to and fro 5-10 times inside the lesion under complete ultrasonic control. With the needle tip still in the lesion, suction was released and the needle was safely retracted inside the needle sheath and locked in a secure position.

All patients had a CT with a 64-slice multidetector CT (Somatom, Sensation 64; Siemens München Germany) and images were obtained with a section thickness of 3 mm with a reconstruction interval of 2-2.5 mm. All cases were analyzed on a workstation with the capability to produce coronal reformatted images. Patients received intravenous (IV) contrast; 120 mL of Conray (Mallinckrodt Baker Inc., St Louis Missouri, United States) was given 45 s prior to the CT examination. Forty milliliters of ioditrat M60 (Justesa Imagen Mexicana) was diluted in 1000 mL of water and given to all patients orally 1 h prior to CT. All patients received IV and oral contrast. All CT images were analyzed by at least two certified radiologists and discussed with the endoscopic team before the procedure (EUS-FNA). All CT and endoscopic studies were performed in the same center.

A pseudotumor (Figure 1) was defined as a non-neoplastic space-occupying lesion, a cause of chronic pancreatitis that may mimic changes typical of pancreatic cancer on CT or endoscopic ultrasound but without histological evidence. It should be recognized, however, that even this definition of "pseudotumor" is highly subjective since it relies on the quality of the preoperative diagnostic evaluation as well as the skills of the interpreters of the tests performed^[10]. A real tumor was defined as a neoplastic space-occupying lesion because of pancreatic cancer confirmed by histology. Clinical characteristics considered associated with chronic pancreatitis were: abdominal pain

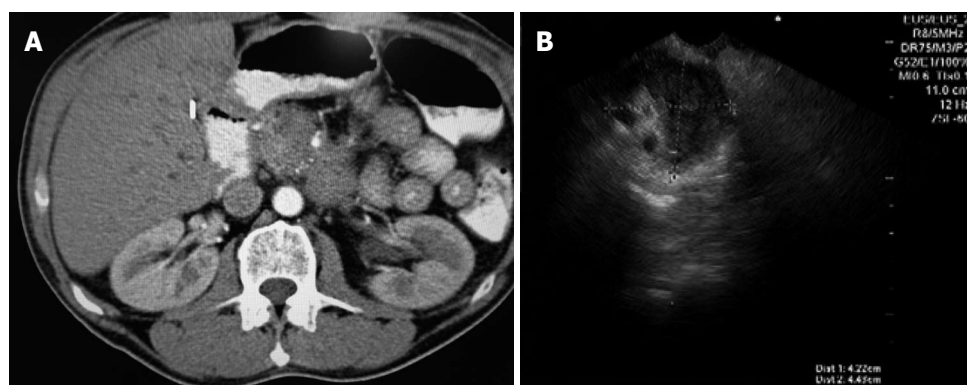


Figure 1 Pseudotumoral chronic pancreatitis in included patient. A: Computed tomography image; B: Endoscopic ultrasound image.

Table 1 Clinical and demographic characteristics of included patients classified by the presence/absence of pseudotumor *n* (%)

	Chronic pancreatitis (<i>n</i> = 26)	Pseudotumoral chronic pancreatitis (<i>n</i> = 9)	<i>P</i> value
Female	5 (19.2)	4 (44.4)	NS
Age, yr ¹	30 (18-74)	53 (18-75)	0.015
Number of EUS criteria ¹	4 (4-8)	4 (4-6)	NS
Follow-up ¹	24 (1-67)	5 (1-35)	NS
Aetiology, alcohol	21 (81)	6 (67)	NS
DM	20 (77)	7 (78)	NS

¹Expressed in median (range). EUS: Endoscopic ultrasound; DM: Diabetes mellitus; NS: Not significant.

Table 2 Imaging characteristics of included patients with pseudotumor and chronic pancreatitis

Patient	Age, yr	Gender	Number of diagnostic criteria for chronic pancreatitis by EUS	Evidence of pseudotumor on CT	Interval ("time between") or follow-up
1	64	F	4	No	1 mo
2	48	F	4	No	13 mo
3	53	M	4	No	21 mo
4	44	F	4	Yes	5 mo
5	75	F	4	Yes	22 mo
6	69	M	4	Yes	13 mo
7	18	M	6	Yes	30 d
8	56	M	5	Yes	30 d
9	52	M	4	Yes	30 d

Time between: Represents the time between diagnosis of pseudotumor and pancreatic cancer; Follow-up: Time of follow-up after diagnosis of pseudotumor without diagnosis of cancer. F: Female; M: Male; CT: Computed tomography; EUS: Endoscopic ultrasound.

in the epigastrium, often with radiation to the back; steatorrhea; and diabetes mellitus^[11].

Statistical analysis

Medians, ranges, and proportions were used to summarize the demographics and clinical variables. Using the χ^2 test or Mann-Whitney *U* test, according variables, differences between groups were tested. A two-tailed *P* value < 0.05 was considered significant. All analyses were per-

formed by SPSS V.20 for Mac.

RESULTS

A total of 200 pancreatic EUS were performed because of clinical suspicion of chronic pancreatitis (abdominal pain in the epigastrium with radiation to the back, or exocrine pancreatic insufficiency with chronic diarrhea and/or steatorrhea). Thirty-five patients with diagnosis of chronic pancreatitis were included. Twenty-six (74.2%) patients were men and 9 (25.8%) patients were women. The median age was 38 years (range 18-75 years). All patients had clinical and EUS criteria. Twenty-two (62.8%) patients had 4 EUS criteria, 6 (17%) patients had five criteria, and 7 (20%) patients had ≥ 6 criteria. Nine (25.7%) patients were diagnosed with pseudotumoral chronic pancreatitis. Clinical and demographic characteristics of included patients classified by the presence/absence of pseudotumoral chronic pancreatitis are shown in Table 1. In Tables 2 and 3, clinical data, demographics, and imaging characteristics of included patients with pseudotumor and chronic pancreatitis are shown.

Two of nine (22.2%) patients with pseudotumoral chronic pancreatitis were diagnosed with pancreatic cancer on follow-up, although basal EUS FNA did not reveal malignant cells. One (11.1%) patient was diagnosed on follow-up with myofibroblastic tumor of the pancreas. The time between the diagnosis of pseudotumoral chronic pancreatitis and pancreatic adenocarcinoma was 35 and 30 d. The diagnosis of myofibroblastic tumor was 30 d after the pseudotumoral chronic pancreatitis diagnosis. The two patients with pancreatic adenocarcinoma had an unresectable pancreatic adenocarcinoma at the moment of final diagnosis. Definitive diagnosis of pancreatic adenocarcinoma was made by surgery. In the remaining six patients with pseudotumoral chronic pancreatitis, the median of follow-up was 11 mo (range 1-22 mo) and they showed no evidence of malignancy on surveillance.

In the follow-up of patients with chronic pancreatitis but without pseudotumoral chronic pancreatitis, none were diagnosed with pancreatic cancer. The median follow-up was 22 mo (range 1-67 mo) (Figure 2).

Table 3 Imaging characteristics of the pseudotumors and final diagnosis

Pseudotumor/ patient	Maximum diameter (mm)	Localization	Vascular involvement	Presence of lymphadenopathy	EUS FNA/adequate sample	Surgery	Final diagnosis
1	35	Body	Yes	No	Normal/yes	No	CP
2	30	Head	No	Yes	CP/yes	No	CP
3	20	Head	No	No	Normal/yes	No	CP
4	35	Head	Yes	Yes	Inflammation/yes	Yes	CP
5	35	Neck	No	No	CP/yes	No	CP
6	28	Body	No	No	CP/yes	No	CP
7	30	Neck	No	Yes	Non-neoplastic cells/yes	Yes	Myofibroblastic tumor
8	40	Head	Yes	Yes	Normal/yes	Yes	Pancreatic cancer
9	40	Head	Yes	Yes	CP/yes	Yes	Pancreatic cancer

CP: Chronic pancreatitis; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

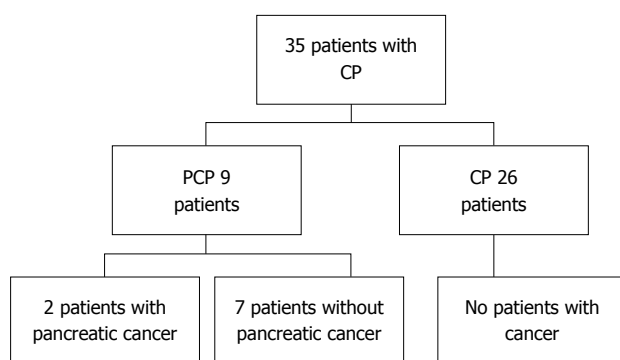


Figure 2 Pseudotumoral chronic pancreatitis and development of pancreatic cancer on follow-up. PCP: Pseudotumoral chronic pancreatitis; CP: Chronic pancreatitis.

Table 4 Frequency of pseudotumoral chronic pancreatitis in patients with chronic pancreatitis according to studies reported in the literature

Ref.	Year	Number of patients (n)	Frequency of pseudotumor	Frequency of pancreatic cancer
Barthet <i>et al</i> ^[12]	1996	85	6%	3.5%
Burski <i>et al</i> ^[8]	2012	436	29%	13%
Current study	2014	35	25%	22%

¹The time between diagnosis of pseudotumor and pancreatic cancer was not reported, only time of survival after diagnosis of pancreatic cancer;

²The time between diagnosis of pseudotumor and pancreatic cancer reported was 4.2 mo.

DISCUSSION

Almost one-third of patients with chronic pancreatitis had pseudotumoral chronic pancreatitis, and two of them (2/9; 22.2%) had unresectable pancreatic adenocarcinoma less than 2 mo after the initial diagnosis. The frequency of pseudotumoral chronic pancreatitis is not well known and little data exist. In one study with 85 patients with chronic pancreatitis, 6% ($n = 5$) of these patients had pseudotumoral chronic pancreatitis and 3.5% ($n = 3$) of them were diagnosed with pancreatic cancer^[12]. In a more recent study, Burski *et al*^[8] found that 29% (125/436) of patients with chronic pancreatitis had pseudotumoral chronic pancreatitis and 13% (16/125) of them were diagnosed with pancreatic adenocarcinoma on follow-up. In Table 4, published data about patients with chronic pancreatitis and pseudotumoral chronic pancreatitis are shown.

Regarding follow-up of patients with pseudotumoral chronic pancreatitis, there are not clear recommendations regarding the ideal imaging study and time for subsequent imaging relative to the initial diagnosis. Therefore, the surveillance for pancreatic cancer in patients with pseudotumoral chronic pancreatitis is not well established and it has a negative impact in this population^[1,13-16]. In this study, in patients with pseudotumoral chronic pancreatitis for whom pancreatic cancer was diagnosed on follow-up, pancreatic cancer was confirmed

at an advanced stage in a period of less than 2 mo after the initial detection. This data suggest a misdiagnosis rather than new onset of the neoplasm during follow-up. Because of that, surveillance programs for pancreatic cancer with intervals greater than 6 mo seem to be insufficient in patients with pseudotumoral chronic pancreatitis. In the study by Burski *et al*^[8], it was concluded that an interval of 3-6 mo for surveillance for pancreatic cancer in patients with pseudotumoral chronic pancreatitis was not optimal due to rapid disease progression. Several studies have attempted to establish EUS imaging criteria (without tissue sampling) for the discrimination of benign inflammatory pseudotumors and tumors. Despite the high resolution of EUS, it does not provide reliable differentiation of benign and malignant lesions of the pancreas^[17]. New technologies, such as EUS elastography and contrast-enhanced EUS (CE-EUS) could be important tools for differential diagnosis. In a multicenter study, 30 cases with benign nodule of chronic pancreatitis were studied with EUS elastography^[18]. All nodules of chronic pancreatitis presented benign aspects (mixed green and low intensity of blue) and elastography showed malignant aspects (intense blue coloration) for all pancreatic adenocarcinomas, endocrine tumors, pancreatic metastases, and pancreatic sarcomas. In the study of Hocke *et al*^[19], adenocarcinoma developed on chronic pancreatitis was non-enhanced after contrast injection. Conversely, pseudotumoral chronic pancreatitis was hypervascularized (91%) after SonoVue® injection. According to our data, older patients with chronic pancreatitis

are at risk of pseudotumoral chronic pancreatitis, and could be candidates for closer follow-up (Table 1).

The limitations of our work are the small sample size and retrospective analysis. The nature of disease makes it difficult for a single center to have a bigger sample size. Multicenter studies must be considered for future designs. Our data are useful for future systematic reviews and meta-analyses.

In conclusion, we suggest that according to specific characteristics of patient, detection of pseudotumoral chronic pancreatitis should lead a close surveillance program for pancreatic cancer with EUS in less than 1 mo or directly to surgical resection. EUS FNA can miss malignancy in nearly 25% of patients with pseudotumoral chronic pancreatitis.

COMMENTS

Background

Pancreatic cancer at diagnosis is unresectable in 70% of cases. It is difficult to differentiate by images between pancreatic carcinoma and pseudotumor in the context of chronic pancreatitis. The authors followed-up patients with chronic pancreatitis and solid pancreatic mass lesions and we assessed the final outcome and identified an optimal surveillance interval.

Innovations and breakthroughs

According to characteristics of patient, detection of pseudotumoral chronic pancreatitis should lead a surveillance program for pancreatic cancer with endoscopic ultrasound fine needle aspiration in < 1 mo or directly to surgical resection.

Peer review

This is an interesting retrospective analysis of patients with pseudotumoral lesions in the context of chronic pancreatitis. The results are alarming.

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