ORIGINAL ARTICLE

Non-alcoholic fatty pancreas disease as a risk factor for pancreatic cancer based on endoscopic ultrasound examination among pancreatic cancer patients: A single-center experience

Cosmas R A Lesmana,*,† [ID] Rino A Gani† and Laurentius A Lesmana*

*Digestive Disease and GI Oncology Center, Medistra Hospital and †Hepatobiliary Division, Department of Internal Medicine, Dr. Cipto Mangunkusumo National General Hospital, Universitas Indonesia, Jakarta, Indonesia

Correspondence
Cosmas R A Lesmana, Digestive Disease and GI Oncology Center, Medistra Hospital, Jl Gatot Subroto Kav 59, Jakarta Selatan 12950, Jakarta, Indonesia.
Email: medicaldr2001id@yahoo.com

[Corrections added on 5 January 2018, after first online publication: The sample size and the number of patients found to have pancreatic malignancy in the 'Abstract' have been updated to tally with the figures reflected in the 'Results' section of the paper, as marked by the symbol ^.]

Abstract

Background and Aim: Non-alcoholic fatty pancreas disease (NAFPD) is a disease that ranges from simple steatosis and can further lead to chronic pancreatitis and possible pancreatic cancer development. Its exact pathogenesis and impact on clinical practice are still largely unknown. Pancreatic cancer is still the most lethal malignancy in the world. Studies about the relationship between NAFPD and pancreatic cancer are still lacking. This study aims to find the possible role of endoscopic ultrasound (EUS) examination as a screening tool in NAFPD patients based on EUS examination among pancreatic cancer patients.

Methods: EUS hospital data were collected within a 2-year period, and all patients who underwent EUS procedures were analyzed. Pancreatic malignancy was diagnosed based on imaging and tumor markers and cytopathology using the endoscopic ultrasound fine needle aspiration (EUS-FNA) procedure. Patients with pre-existing pancreatic diseases, significant alcohol consumption, or other primary cancer with metastasis to the pancreas were excluded. Statistical analysis was performed using SPSS version 23.0.

Results: In total, 162 patients (75 females and 87 males) were recruited for database analysis.^ Pancreatic malignancy was found in 43 (26.5%) patients, whereas fatty pancreas was found in 53 (32.7%) patients, and this was commonly found among pancreatic cancer patients.^ Based on logistic regression analysis, factors such as age, gender, diabetes, and chronic pancreatitis were not found to be significant risk factors for pancreatic malignancy where fatty pancreas is the only significant risk factor for pancreatic cancer (odds ratio: 18.027 [95% CI: 7.288–44.588]).

Conclusion: Prevalence of NAFPD among pancreatic cancer patients is high. Future studies can be conducted to show whether EUS can be considered a screening tool for the early detection of pancreatic malignancy in NAFPD patients; a cohort prospective study might also be needed to show clear causality between fatty pancreas and pancreatic cancer.

Introduction

Pancreatic cancer is still the most lethal cancer in the world as it has a very low survival rate and the worst prognosis. It has been postulated that chronic pancreatitis is a major risk for the development of pancreatic cancer.[1,2] However, metabolic conditions such as obesity and diabetes mellitus (DM) have also been considered risk factors for pancreatic cancer. The prevalence of obesity and DM has recently been increasing in most Asian countries, especially with the new entity that is now well known as non-alcoholic fatty liver disease. On the contrary, there has been a controversial study about DM as a risk factor for pancreatic cancer. This might

be because not all patients with an insulin resistance condition demonstrate further disease progression to DM.[3–5]

Non-alcoholic fatty pancreas disease (NAFPD) is a new clinical entity where there is evidence of significant fatty infiltration in the pancreas parenchyma without any significant alcohol consumption. The clinical pathway from simple fatty infiltration of the pancreas, the steato-pancreatitis condition, to the possibility of pancreatic cancer development has not been well studied yet. However, it has been hypothesized that this condition is closely related to the insulin resistance condition.[6,7]

Fatty pancreas is a common incidental finding during transabdominal ultrasound examination. The impact of this finding has

been unexplored in gastroenterology practice due to the unknown outcome of follow up. The difficulty of visualizing the pancreas has also become another reason to ignore this symptom in asymptomatic patients. Advance imaging, such as an abdominal computed tomography (CT) scan or magnetic resonance imaging (MRI), cannot be used routinely to examine pancreas in daily practice as it would be too costly in the medical check-up setting.[6]

Endoscopic ultrasound (EUS) is the best method to examine the pancreas, but it is still unethical to use it as a screening tool because of the cost and because it has been considered an advance endoscopic procedure.[8]

This study aimed to demonstrate the possible role of the EUS screening examination in the early detection and surveillance of a fatty pancreas condition based on patients with pancreatic cancer diagnosed through EUS examination.

Methods

This was a retrospective EUS database study in Medistra hospital within a 2-year period. Medistra hospital is the most referred private hospital. All patients (with and without pancreatic cancer) who underwent EUS procedures were recruited consecutively. Pancreatic malignancy was diagnosed based on imaging and tumor marker and cytopathology using the EUS-FNA procedure. Fatty pancreas is defined based on contrast echo (bright or hyperechoic pancreas) between the pancreas and kidney. The cancer pathology assessment was performed by two pathologists who were blinded to clinical data. Several metabolic factors, including the presence of fatty pancreas or pancreatic lipomatosis, were analyzed. Patients with pre-existing pancreatic diseases, significant alcohol consumption, or other primary cancer with metastasis to the pancreas were excluded. The EUS procedures were performed by a consultant gastroenterologist who had 10 years of experience in advanced endoscopic procedures and transabdominal ultrasound procedures. The EUS equipment included an Olympus JF UCT 180 EUS scope (Olympus, Japan), which was connected to an Aloka IPF-1701C ultrasound machine (Aloka, Tokyo, Japan). Statistical analysis was performed using SPSS version 23.0 (IBM, New York, NY, USA).

Results

In total, 162 patients (75 females and 87 males) were recruited for the database analysis. Pancreatic malignancy was found in

Table 1 Patients' EUS hospital data

Variables	Frequency	Percentage (%)
Age (mean SD) years	57±15.9	
Gender		
Male	87	53.7
Female	75	46.3
Diabetes mellitus	28	17.3
Chronic pancreatitis	45	27.8
Pancreatic lipomatosis	53	32.7
Pancreatic cancer (all)	43	26.5
IPMN	5	11.6
Adenocarcinoma	35	81.4
Neuroendocrine tumor	3	8.0

EUS, endoscopic ultrasound; IPMN, Intra Papillary Mucinous Neoplasm.

43 (26.5%) patients, whereas fatty pancreas was found in 53 (32.7%) patients, and this was commonly found among pancreatic cancer patients. Most of the pancreatic cancer was dominated by adenocarcinoma type (81.4%). (Table 1) Based on cross-sectional EUS data, pancreas lipomatosis was dominant in patients with pancreatic cancer (Table 2). Of 43 pancreatic malignancy patients, 2 had diabetes and 7 had diabetes and fatty pancreas. Based on logistic regression analysis, factors such as age, gender, diabetes, and chronic pancreatitis were not found to be significant risk factors for pancreatic malignancy, where fatty pancreas was the only significant risk factor for pancreatic cancer (odds ratio: 18.027 [95% CI: 7.288–44.588]) (Table 3).

Discussion

To our knowledge, this is the first study in Asia with quite a big sample of patients looking at the possible role of EUS examination as a screening tool of fatty pancreas based on pancreatic cancer patients.

Our study showed significant difference between pancreatic cancer prevalence and the worldwide statistic data.[2] This finding might be because our private hospital is the most referred private hospital for hepatopancreatobiliary diseases, and some patients who were referred to us were already suspected to have pancreatic malignancy. The possibility of selective bias has been overcome by consecutive subjects' collection. This finding has provided important messages for clinicians about pancreatic cancer awareness and the importance of screening surveillance or early detection in their clinical practice as most of pancreatic cancer patients are already in the advanced stage of the disease at the time of diagnosis. It is well known that the early detection of pancreatic cancer is still difficult because most patients are either asymptomatic or do not have any specific symptoms, such as nausea, bloating, back pain, and abdominal pain. Most of them usually present with jaundice due to bile duct obstruction, and this symptom is a sign of advance disease. Another major drawback is that early screening is also difficult due to its anatomical location.[9] The most routine biomarker used, CA 19-9, is considered not to be clinically effective because of the wide range of sensitivity and specificity (68–90%). It can be also be at a high level due to other causes, such as cholangitis, biliary cancer, and gastrointestinal cancer. The other biomarkers are still not ready for use in daily practice due to technique difficulty, possible selective bias in training set due to a higher level of the samples, and genetic heterogeneity. Imaging such as abdominal CT scan and MRI also have high sensitivity and specificity. However, the radiation risk and contrast agent exposure during CT examination makes this modality not suitable for routine screening and surveillance. The long durability of MRI examination time and the cost also become debatable matters when using this modality for early detection and screening in general population.[9–11]

Based on our findings, there is a high prevalence of fatty pancreas found incidentally among pancreatic cancer patients. It has been reported that there is higher fatty infiltration at the pancreas among patients with pancreatic ductal adenocarcinoma (PDAC) who underwent surgery when compared to other biliary cancers.[12] Fatty infiltrations in the pancreas are hypothetically based on two mechanisms, which include acinar cell disruption and increase of intracellular triglycerides, which lead to fat accumulation. It is usually initiated by a high level of free fatty acid,

Table 2 Characteristics of patients with and without pancreatic cancer

Variable	No pancreatic cancer (*n* = 119)	Pancreatic cancer (*n* = 43)	*P* value
Age (median, interquartile range), years	52 (24)	62 (21)	*P* = 0.026 (Mann–Whitney)
Age (years)			
< 60	71 (59.7)	17 (39.5)	*P* = 0.023
≥ 60	48 (40.3)	26 (60.5)	
Gender (*n*, %)			
Male	60 (50.4)	27 (62.8)	*P* = 0.212
Diabetes mellitus (*n*, %)			
Yes	19 (16.0)	9 (20.9)	*P* = 0.484
No	100 (84.0)	34 (79.1)	
Pancreas lipomatosis (*n*, %)			
Yes	19 (16.0)	34 (79.1)	*P* = 0.001
No	100 (84.0)	9 (20.9)	
Chronic pancreatitis (*n*, %)			
Yes	34 (28.6)	11 (25.6)	*P* = 0.843
No	85 (71.4)	32 (74.4)	

Table 3 Bivariate and multivariate analysis (logistic regression)

Variables	*P*	Odds ratio	95% CI
Bivariate analysis			
Age	0.004	1.039	1.012–1.066
Gender	0.165	1.659	0.812–3.393
Diabetes mellitus	0.462	1.393	0.576–3.370
Chronic pancreatitis	0.708	0.859	0.389–1.898
Pancreatic lipomatosis	0.001	19.883	8.219–48.100
Multivariate analysis			
Age	0.113	1.028	0.993–1.065
Gender	0.136	2.001	0.805–4.976
Pancreatic lipomatosis	0.001	18.027	7.288–44.588

which is mostly seen in patients with obesity. The imbalance of adipokines will further lead to oxidative stress where there are increases of pro-inflammatory cytokines, such as tumor necrosis factor alpha, interleukin-6 (IL-6), monocyte chemotactic protein-1 combined with macrophages producing IL-1b, and myeloperoxidase. Progression of obesity will lead to excessive fat accumulation in most non-adipose tissue, such as the liver, pancreas, skeletal muscle, and heart. Possible chronic inflammation with excessive fat accumulation would further lead to cell injury and cancer development.[13] Our study was not a prospective cohort study as fatty pancreas patients were followed until the development of pancreatic cancer. This study's results may demonstrate more association between fatty pancreas and pancreatic cancer, but the association is strong based on bivariate and multivariate analysis. On the other hand, it is still a matter of debate which fatty pancreas patients we should follow up for screening or surveillance. A similar troublesome issue arises when fatty liver becomes more prevalent. Primary considerations, such as pancreatic incidence rate, possibility and outcome of surgical resection rate in early cancer, median survival after chemotherapy, and progression metastasis of the disease, and secondary considerations, such as cost of the examination, invasiveness, availability, and the man behind the gun based on training and experience, still need to be comprehensively reviewed in clinical practice.

There are some limitations to this study. First, this was only a cross-sectional database analysis between pancreatic cancer and fatty pancreas, but the association between these two variables has delivered a very important message and supported most of the previous studies about the possibility of fatty pancreas being an important risk factor for cancer development in daily practice, thus making clinicians more aware. In fact, there is still no clear pathogenesis mechanism in this matter. Second, we did not analyze other metabolic factors such as lipid profile, body mass index, central obesity, and blood pressure, but these metabolic factors have not yet been proven to have a direct association with pancreatic cancer; yet, it is fatty pancreas that has been considered a new independent risk factor where it is preceded by high free fatty acid accumulation due to obesity or central obesity. We also did not include smoking as a risk factor in our study, but all of our pancreatic cancer patients did not have any significant heavy smoking habit. Third, the fat in the pancreas was not quantified by MRI examination; however, EUS is still the most sensitive tool to screen the pancreas, and there is no consensus yet about the best pancreatic fat quantification other than biopsy through open surgery.[14–16] Our study also analyzed patients who were already diagnosed with primary pancreatic cancer. The diagnosis of pancreatic malignancy based on pathology examination makes our study qualified to rule out the possibility of secondary or metastatic disease. Until now, there is also no consensus about how we diagnose fatty pancreas in routine clinical practice, but it would still need a prospective cohort study to conduct long-term follow up in patients with fatty pancreas. It is also not ethical at this moment to do routine EUS follow-up studies as we require more data and clearer pathogenesis between these interaction conditions. In fact, there is no study yet that has findings that coincide with the results of our study.

Conclusions. There is a high prevalence of NAFPD detected among pancreatic cancer patients when compared to nonpancreatic cancer patients. Further studies, such as a prospective cohort study as well as what has been done in most of NAFLD studies, are needed to find more clear pathogenesis and the time frame of cancer development among NAFPD patients in order to provide the exact time to do an EUS follow up study for screening and surveillance.

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