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Clinical features and outcomes of total pancreatic lipomatosis with chronic pancreatitis: a case series

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Abstract

Background Fatty changes in the pancreas are common, whereas total pancreatic lipomatosis (PL) is rare. Commonly associated with various components of metabolic syndrome and metabolic-associated steatotic liver disease, total PL can have various etiologies and can manifest with severe pancreatic exocrine insufficiency.

Method We retrospectively analysed the clinical profile and management outcomes of 8 patients (mean age: 37.1 years; 5 male) with total PL seen at a tertiary care center over the last 15 years.

Results All patients presented with abdominal pain and had coexistent chronic pancreatitis, while 5/8 (62%) patients had metabolic syndrome. None of the patients had a history of acute pancreatitis or congenital syndromes, nor developed pancreatic carcinoma in the follow up. Seven (87%) patients had pancreatic ductal dilatation and calcification. All patients had pancreatic exocrine insufficiency, while 5/8 (52%) patients had endocrine insufficiency. Six (75%) patients were successfully managed with pancreatic endotherapy.

Conclusions Pancreatic endotherapy is safe and effective in the treatment of abdominal pain in patients who have chronic pancreatitis with total PL. These patients have a high frequency of pancreatic exocrine as well as endocrine insufficiency.

Keywords Chronic pancreatitis, fatty pancreas, endosonography, diabetes

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Introduction

There have been numerous terminologies for the accumulation of fat in the pancreatic gland: pancreatic lipomatosis (PL), fatty infiltration, fatty replacement, fatty pancreas, lipomatous pseudohypertrophy, nonalcoholic fatty pancreatic disease, nonalcoholic fatty pancreato-steatosis, and pancreatic steatosis [1]. The term PL has been used to describe fatty replacement of exocrine pancreatic tissue and fat infiltration [1]. The fatty replacement could be either focal or total, with focal replacement being the most common. Total PL is a very rare condition in which there is complete fatty replacement of the pancreatic parenchyma, and this may result in pancreatic exocrine insufficiency [2-4].

The exact etiopathogenesis of PL is unclear, but several predisposing factors have been described, including metabolic diseases (diabetes mellitus, obesity, dyslipidemia, severe malnutrition, Cushing syndrome), congenital anomalies of the pancreas, cystic fibrosis, iron overload conditions such as hemochromatosis, drugs, viral infections (hepatitis B virus, reoviruses, human immunodeficiency virus), chronic pancreatitis and pancreatic duct blockage [5]. Most patients with PL remain asymptomatic, but extensive fat replacement, as in total PL, can result in impairment of pancreatic exocrine or endocrine function [4].

Total or extensive PL has rarely been reported following pancreatic duct obstruction by calculi or carcinoma [6-8]. There is a paucity of literature on the clinical features and outcomes of total PL associated with chronic pancreatitis. In the current case series, we retrospectively analyzed the clinical

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and imaging features, as well as the treatment outcomes, in 8 patients with chronic pancreatitis and total PL.

Patients and methods

The database of patients with chronic pancreatitis seen in our unit over the last 15 years was retrospectively searched for patients who had total PL.

Study definitions

Total PL: complete replacement of the pancreatic parenchyma by fat (low attenuation value) with no demonstrable pancreatic parenchyma on computed tomography (CT) of the abdomen.

Chronic pancreatitis: diagnosed in the presence of appropriate clinical symptoms, imaging findings, and/or endoscopic ultrasound (EUS) findings. Imaging diagnosis using CT and/or magnetic resonance imaging was based on the Cambridge classification of chronic pancreatitis, whereas EUS diagnosis was based on the Rosemont criteria [9-11].

Pancreatic exocrine insufficiency: diagnosed when fecal elastase values were ≤200 μg/g stool [12].

Pancreatic endocrine insufficiency: diagnosed when either glycosylated hemoglobin (Hba1c) was ≥6.5 g/dL or fasting blood sugar was >126 mg/dL [13].

Detailed clinical, laboratory, imaging and treatment data for patients with chronic pancreatitis and total PL were retrieved from the database. The presence of steatorrhea, glycemic status, metabolic abnormalities and details of endoscopic/surgical interventions, if any, were retrieved. Patients with abdominal pain were treated as per the unit's management protocols, including initial medical therapy followed by interventional therapy in non-responders. The medical therapy included antioxidants, nonsteroidal anti-inflammatory drugs, pancreatic enzyme supplements, and pregabalin or selective serotonin reuptake inhibitors. The interventional therapy protocol included initial pancreatic endotherapy followed by surgery in non-responders. Patients with endocrine insufficiency were treated with either oral hypoglycemic agents or insulin therapy, at the discretion of the treating endocrinologist. Pancreatic endocrine insufficiency was treated with pancreatic enzyme replacement therapy.

Results

Over the last 15 years, 8 patients (mean age: 37.1±5.5 years; 5 male) with total PL and chronic pancreatitis were seen in our unit (Table 1). Two (25%) patients had a history of significant alcohol consumption, whereas in 6 (75%) patients no underlying etiology could be identified (idiopathic chronic pancreatitis). One patient with underlying alcohol-related chronic pancreatitis also had a history of significant smoking. All patients presented with chronic upper abdominal pain of

Table 1 Characteristics of the patients included in the present case series

#	Age	Sex	Etiology	Diabetes mellitus	Hypertension	Serum triglycerides (mg/dL)	HDL (mg/dL)	BMI (kg/m^2)	Fatty liver	Calcification	Duct dilatation	Steatorrhea	Fecal elastase*
1	34	F	Idiopathic	Yes	Yes	154	36	26.41	No	Yes	Yes	No	78
2	38	F	Idiopathic	Yes	Yes	170	42	24.11	No	Yes	Yes	No	112
3	41	M	Idiopathic	Yes	Yes	240	28	24.09	yes	Yes	Yes	no	160
4	29	M	Idiopathic	No	No	270	48	19.11	No	Yes	Yes	no	40
5	31	F	Idiopathic	No	No	312	30	21.82	No	Yes	Yes	no	160
6	42	M	Alcohol	Yes	No	130	29	25.76	yes	Yes	Yes	yes	20
7	37	M	Idiopathic	No	No	146	48	22.14	No	No	Yes	no	340
8	45	M	Alcohol	Yes	Yes	180	35	25.17	yes	Yes	Yes	no	118

**μg/g of stool*
HDL, high-density lipoprotein; BMI, body mass index

3-26 months duration. None of the patients had a history of prior acute pancreatitis. Two (25%) patients were overweight and 3 (37.5%) patients were obese, as per the Indian Consensus Group 2009 criteria [14]. Pre-existing hypertension was recorded in 4 (50%) patients, whereas 5 (62.5%) patients had pre-existing diabetes. Steatorrhea at presentation was observed in 1 (12.5%) patient.

Six (75%) patients had elevated serum triglyceride levels (>150 mg/dL) at presentation. Seven (87.5%) patients had low fecal elastase, while 3/8 (37.5%) patients had severe exocrine insufficiency (fecal elastase <100 μg/g of stool). Seven (87.5%) patients had pancreatic calcification, and all 8 patients had a dilated main pancreatic duct observed on the abdominal CT. All 8 patients had complete replacement of the pancreatic parenchyma by fat (low attenuation value), with no demonstrable pancreatic parenchyma on CT (Fig. 1, 2). Magnetic resonance imaging (MRI) was performed in 3 patients and revealed a hyperintense pancreas on T2-weighted images, suggestive of total PL, along with a dilated main pancreatic duct. EUS revealed an echogenic pancreas (Fig. 1) in all the patients. The pancreatic duct was well visualised on EUS in 5/8 (62.5%) patients, while pancreatic calcification could be detected in 3 patients. No other EUS features of chronic pancreatitis could be identified in these patients.

Fatty liver was detected on imaging in 3 patients, of whom 2 had elevated liver enzymes. However, both these patients also had a history of significant alcohol consumption. The abdominal pain was successfully managed with medical therapy in 2 (25%) patients, while 6 (75%) patients were successfully managed with pancreatic endotherapy. No adverse effects of pancreatic endotherapy were encountered in these patients. None of the patients required surgery and none developed pancreatic malignancy on follow up. The patient with steatorrhea was successfully managed with pancreatic enzyme replacement. Two patients with diabetes required insulin therapy, while 3 patients were managed with oral hypoglycemic drugs.

Discussion

Total PL is a rare condition of the pancreas that results in its complete fatty replacement; it has been infrequently reported in patients with chronic pancreatitis. In the current case series, we report the clinical profile as well as treatment outcomes in 8 patients who had total PL coexistent with chronic pancreatitis. The majority of our patients (5/8) were males and the mean age was 37 years. In addition, the majority of our patients had a coexistent component of metabolic syndrome, such as hypertension, diabetes, obesity or dyslipidemia. Sepe *et al* also reported that the presence of any metabolic syndrome components, such as a body mass index (BMI) ≥30 kg/m^2, hyperlipidemia, diabetes or hypertension, increased the prevalence of fatty pancreas by 37% (odds ratio 1.37, P=0.01), while factors independently associated with fatty pancreas on multivariate analysis were an elevated BMI and the presence of fatty liver [15]. In our case series, one third of our patients had coexistent fatty liver. Alcohol consumption and smoking have also been reported to be risk factors for a fatty pancreas [16,17]. Two of the 8 patients with total PL in our case series had a history of significant alcohol consumption, while 1 of them also had a history of significant smoking.

Whether chronic pancreatitis precedes fatty changes in the pancreas, or is an effect of obstruction of the pancreatic duct, cannot be ascertained with certainty. It has been postulated that long-standing obstruction to the pancreatic duct leads to lipomatous changes, but the exact mechanisms need to be elucidated. An animal study on the effects of ductal ligation reported that the volume of the pancreas increased in the first 2 days, as a result of interstitial edema, followed by a rapid decrease due to atrophy of the exocrine tissue [18]. The ductal cells, however, proliferated, with mitotic figures forming duct-like structures lacking in the acinar cells. After 2 weeks, the ductal cells also started decreasing in number, and the pancreas then showed intralobular fatty replacement, resulting in its gradual enlargement to a size approximating normal 8 weeks after duct ligation.

The symptoms of PL range from none, to non-specific abdominal pain, to severe pancreatic exocrine insufficiency presenting as chronic diarrhea [3]. In our series, all the patients had presented with abdominal pain, while only 1 patient had symptomatic exocrine insufficiency in the form of steatorrhea, which responded to pancreatic enzyme replacement therapy. Despite the absence of symptoms, 7 (87.5%) patients had low fecal elastase and 3 (37.5%) patients had very low fecal elastase levels (<100 μg/g of stool). The abdominal pain present in our patients was due to coexistent chronic pancreatitis resulting

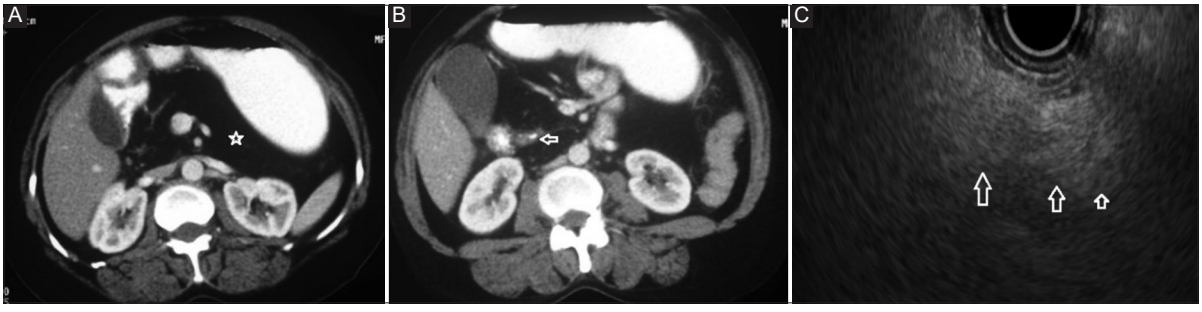

Figure 1 (A) Computed tomography (CT) of abdomen: complete replacement of pancreas by fat (low attenuation value*). (B) CT abdomen: calcification in head of pancreas (arrow). (C) Endoscopic ultrasound: increased echogenicity of pancreas

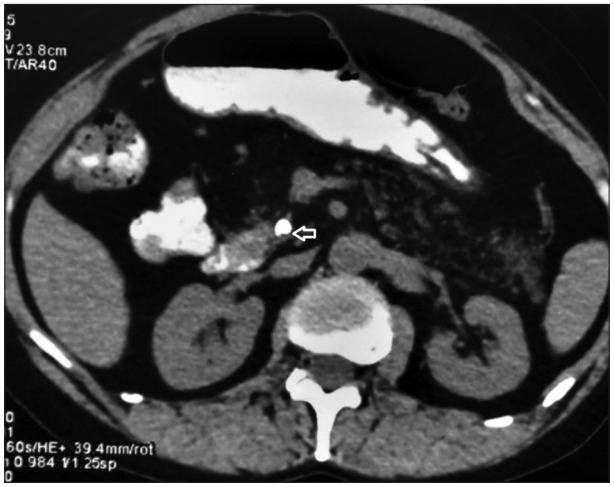

Figure 2 Computed tomography (CT) of abdomen: complete replacement of pancreas by fat with scattered islands of pancreatic parenchyma in body and tail. Calcification also noted in head (arrow)

in ductal hypertension, and fatty replacement of the pancreas was probably not responsible for the abdominal pain. Fatty replacement of the pancreas has also been associated with reduced insulin secretion and the development of diabetes mellitus [19,20]. A study has shown that the presence of >25% fat infiltration of the pancreas is associated with a significantly increased risk of diabetes as well as atherosclerosis [21,22].

Ultrasound findings in fatty pancreas are often nonspecific and inconclusive, because the fatty change results in increased echogenicity and hence a hyper-reflective pancreas, making sonographic assessment difficult. In addition, the overlying bowel gas and abdominal fat cause difficulty in visualizing the pancreas [2,3]. Non-contrast CT can diagnose total PL by revealing specific fat density in the pancreatic bed, and demonstrating a negative attenuation value of pancreatic parenchyma that is replaced by the fat. However, the pancreatic parenchyma trapped between fatty tissues can show enhancement on contrast CT, simulating a pancreatic mass [23]. In these situations, MRI has the advantage over CT of demonstrating uneven fatty replacement of the pancreas [3]. In our series, all 8 patients had complete replacement of the pancreatic parenchyma by fat (low attenuation value), with no demonstrable pancreatic parenchyma on CT, and MRI revealed a hyperintense pancreas on T2-weighted images, suggestive of total PL, along with a dilated main pancreatic duct in 3/3 patients.

Because of its rarity, there are no consensus treatment guidelines or any specific treatment for total PL associated with chronic pancreatitis [1,3]. While lifestyle modifications have been shown to reduce the extent of pancreatic steatosis, their effect on total PL is unclear. There is also a paucity of prospective studies on the long-term follow up of patients with total PL. Their management revolves around the improvement of maldigestion, as well as nutrient deficiencies, treatment of diabetes and the management of chronic pancreatitis and its local complications, including control of pain. Oral pancreatic enzyme replacement therapy is effective for the management of maldigestion. Patients with coexistent metabolic syndrome can benefit from weight reduction, control of diabetes/blood pressure, regular exercise and management of dyslipidemia [3,24]. In our series, exocrine and endocrine insufficiency was successfully managed with pancreatic enzyme replacement and oral hypoglycemic drugs/insulin, respectively. The abdominal pain was successfully managed with medical therapy in 2 (25%) patients and by pancreatic endotherapy in 6 (75%) patients, and the presence of PL did not appear to impact the response to pancreatic endotherapy.

Our case series had important limitations, including a small sample size, its retrospective and single-center design, and the potential for selection bias.

In conclusion, total PL associated with chronic pancreatitis is a rare condition, and these patients have a high frequency of both pancreatic exocrine and endocrine insufficiency. Pancreatic endotherapy is safe and effective in the treatment of abdominal pain in patients who have chronic pancreatitis with total PL.

Summary Box

What is already known:

- Total pancreatic lipomatosis (PL) is a very rare condition in which there is complete fatty replacement of the pancreatic parenchyma; this may result in pancreatic exocrine insufficiency
- Total or extensive PL has been rarely reported following pancreatic duct obstruction by calculi or carcinoma

What the new findings are:

- Chronic pancreatitis associated with total PL coexists with metabolic syndrome features such as hypertension, diabetes, obesity and dyslipidemia
- These patients present with pain, and have a high incidence of endocrine and exocrine insufficiency
- Pancreatic endotherapy is safe and effective in the treatment of abdominal pain in patients who have chronic pancreatitis with total PL

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