FATTY LIVER DISEASE AFTER PANCREATODUODENECTOMY AND TOTAL PANCREATECTOMY

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Annotation

Pancreatoduodenectomy is the only treatment method for patients with pancreatic head and periampullary region tumors. It is known that some long-lived patients develop exocrine pancreatic insufficiency after surgery. One of the consequences of exocrine pancreatic insufficiency is fatty liver disease, which has been reported to occur in 7.8% to 40.0% of patients after pancreatoduodenectomy. We reported two clinical cases of patients who underwent pancreatoduodenectomy and total pancreatectomy for pancreatic head cancer and intraductal papillary mucinous neoplasm of the main pancreatic duct. After surgery, they developed rapidly progressive fatty liver disease with no history of liver disease, leading to death from liver failure 20 days and 3 months after surgery. Severe malnutrition caused by exocrine pancreatic insufficiency, postoperative eating disorders, and exacerbation of diabetes mellitus were the main factors contributing to the rapid deterioration of the condition. This clinical case highlights the possibility of developing life-threatening fatty liver disease with severe fibrosis after pancreatoduodenectomy and total pancreatectomy. Careful monitoring of liver status, regular nutritional assessment of patients, prophylactic replacement of pancreatic enzymes, and ensuring adequate nutrition are important.

Introduction

Pancreatoduodenectomy (PD) is the only available treatment for patients with tumors of the pancreatic head and periampullary zone. Due to the malignant potential of these tumors, overall survival after PD remains generally unsatisfactory, although some long-term survivors have been described.[1,2] It is known that some long-term surviving patients develop exocrine pancreatic insufficiency (EPI).[3,4] One of the consequences of EPI is fatty liver disease (FLD), which has been reported to occur in 7.8% - 40.0% of patients after PD.[5,6]

Possible risk factors for the development of FLD include pancreatic fistula,[7] lack of insulin use,[8] postoperative loss of body mass index (BMI),[8] volume of surgical blood loss,[9] low remnant volume of the pancreas,[6,10] postoperative diarrhea,[6] infection,[10] female gender, cancer of pancreatic head,[6] and postoperative EPI,[11] but none of these factors has been found to be fully responsible for the occurrence of FLD. In addition, no methods have been developed for the prevention and treatment of FLD after PD. *Brown JA et. al.* reported that reduced remnant pancreatic volume after PD influences the development of FLD.[12]

Some studies suggest that malnutrition or malabsorption of essential nutrients caused by EPI leads to FLD.[13,14] Changes in metabolism resulting in hepatic steatosis could lead to sensitivity for hepatocyte damage, inflammation, and fibrosis.[12,15] Administration of pancreatic enzymes as a treatment for EPI has a beneficial effect on post-PD FLD,

suggesting that EPI may be the primary cause of new-onset FLD in these patients.[13,15] Other evidence of malnutrition in patients with EPI or post-PD is the report of increased serum taurine levels and decreased serum levels of methionine, tyrosine, albumin, cholinesterase, zinc, and total cholesterol.[13,15] Therefore, other nutrients or mechanism that not yet have been identified could cause the hepatic steatosis. Besides little evidence indicating that FLD could be treated with pancreatic enzyme administration, adequate treatment is not yet recognized.

The pancreas plays a central role in the absorption of essential nutrients. Its dysfunction causes various abnormalities in the body, notably in metabolic cascades in the liver. It has been previously documented that severe hepatic steatosis sometimes occurs in pancreatectomized patients.[16,17] However, the clinicopathological characteristics of this type of FLD have not been fully investigated.

FLD is characterized by two steps of liver injury: intra hepatic lipid accumulation (hepatic steatosis) and inflammatory progression to FLD (i.e., the two-hit theory).[18] The first hit is fat accumulation in hepatocytes in the setting of obesity, type II diabetes, and hyper lipidemia, leading to development of hepatic steatosis. A second hit, including oxidative stress, inflammatory cytokines, and endotoxins, isconsidered to activate inflammatory cells, leading to progression of simple hepatic steatosis to FLD. This or is well known as pathogenesis of FLD associated with obesity and metabolic syndrome.

The gold standard for diagnosis of hepatic steatosis is a liver biopsy.[19,20] However, biopsies are only performed when the result significantly influences therapeutic options and non-invasive alternatives have not provided sufficient information. Studies have investigated the use of imaging modalities (US, CT and MRI) as non-invasive means to assess hepatic steatosis. Ultrasound is simple to employ but has limitations in both sensitivity and accuracy.[19] CT and MRI provide higher sensitivity and thus are better alternatives.[19,20]

There are few publications worldwide regarding the development of FLD after major pancreatectomy. The previous study by *Cools, C et al.* reported that 14 (33%) of the 42 patients who underwent PD developed hepatic steatosis (liver-to-spleen CT attenuation ratio less than 0.9), which is currently known as FLD.[21] *Okabe, H et al.* reported, that 54 patients underwent PD in our department, and 20 (37%) of them developed FLD (hepatic CT value \ 40 HU) after surgery.[22] The most recent study by *Imaoka, H et et al.* reported that the incidence of FLD after PD (liver-to-spleen CT attenuation ratio less than 0.9) was 23% (14 of 60 patients) and liver biopsy of 8 patients showed FLD. However, FLD is still a little-known complication after PD, and the mechanism of development of FLD after PD remains unclear.[9]

Here we describe 2 cases of rapidly progressive and fatal fatty liver disease that developed shortly after PD and total pancreatectomy without concomitant liver disease.

Clinical presentation

Case 1

Patient I., 67 years old, was admitted to the Syzganov National Scientific Center of Surgery, Department of hepatopancreatobiliary surgery and liver transplantation with a diagnosis of a tumor of the pancreatic head. It is known from the medical history of the disease that the patient has been ill since July 2022, when she began to complain of pain in the epigastrium and right hypochondrium, general weakness, dry mouth, and nausea. After 1 week, the patient's general condition worsened, pain in the epigastric region increased, complaints of jaundice of the skin and sclera, and acholic stools joined.

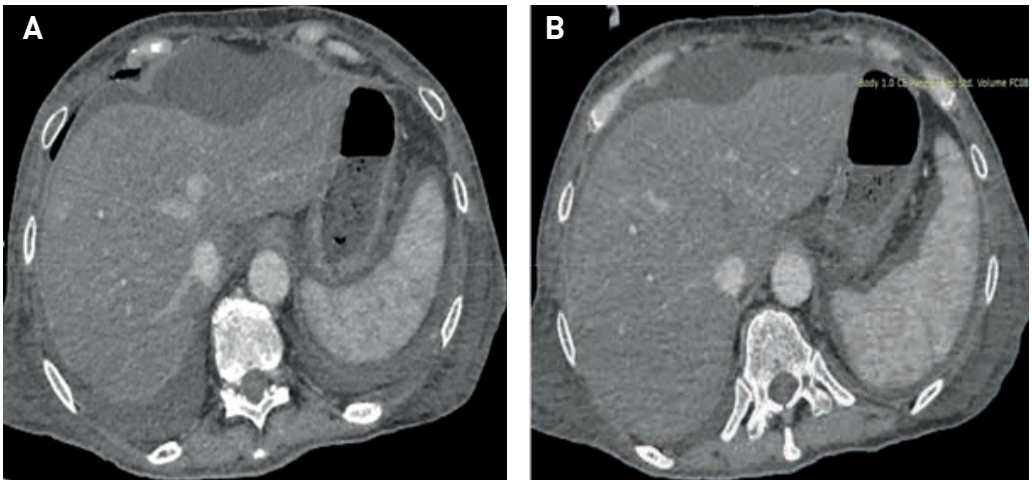
She was urgently hospitalized with the clinic of obstructive jaundice in one of the hospitals in Almaty. At that time, the total bilirubin level in the analyzes was 269 mmol/l. The patient underwent surgical treatment in the following volume: percutaneous transhepatic biliary drainage under ultrasound control. The dynamics of total bilirubin decreased to 135mmol/l. (Table 1) After that, the patient was sent to our clinic for examination and radical surgical treatment. On admission, the patient's condition was stable. During the examination, a contrast-enhanced CT scan revealed a tumor originating from the head of the pancreas.

Table 1.
Data on laboratory tests after surgery

	Day 18	Day 19	Day 20
Total bilirubin (normal level 4.0-20,5 mmol/l)	28.2	58.7	128.4
Direct bilirubin (normal level 0.0-5.1 mmol/l)	24.8	39.4	85.6
Prothrombin index (normal level 180.0-110.0%)	42.9	50.9	50.0
INR(normal level 0.8-1.4)	1.6	1.5	1.5
White blood cells (norma llevel 4.0-9.0 10^9/l)	7.8	14.8	30.2

After preparation, laparotomy and standard PD were performed under general anesthesia. Pancreatojejunostomy was performed using a modified Blumgart method using the duct-to-mucosa method. The histopathologic diagnosis is a morphologic picture of a moderately differentiated ductal adenocarcinoma of the pancreatic head with negative resection margins. On the 2nd day water intake was started, and 4 days after the operation a fat-restricted diet was started. Pancreatic fistula was not observed. Large losses of ascites fluid were noted through drainage tubes from the abdominal cavity, and albumin therapy was performed. After the operation, the biochemical parameters of liver function returned to normal. However, on the 18th day after the operation, biochemical parameters of liver function, white blood cells in the blood began to increase, and coagulopathy was observed. The patient's general condition worsened, she was prone to hypotension (arterial pressure – 60/40 mmHg), and hemodynamics was unstable. After that, the patient was transferred and received treatment in the department of anesthesiology and intensive care. (Figure 1)

Figure 1.
Contrast-enhanced computed tomography of clinical case 1.



A- B Postoperative computed tomography showed signs of pronounced fatty liver disease, where there was a diffuse decrease in liver parenchyma density+22+34 HU units, and the presence of ascites.19th day after surgery.

On the 19th, the patient underwent contrast-enhanced computed tomography, which showed a diffuse decrease in liver parenchymal density, the presence of as-cites, and signs of FLD. The patient's general condition gradually deteriorated. The subsequent clinical course of liver dysfunction worsened, and the patient developed severe liver failure with increasing hyperbilirubinemia. She died of FLD on the 22nd day after surgery. Histologic examination revealed marked fatty tissue with microdroplets and large droplets, signs of fibrosis, balloon degeneration of hepatocytes, and fatty deposits suggestive of hepatitis or FLD. (Figure 2)

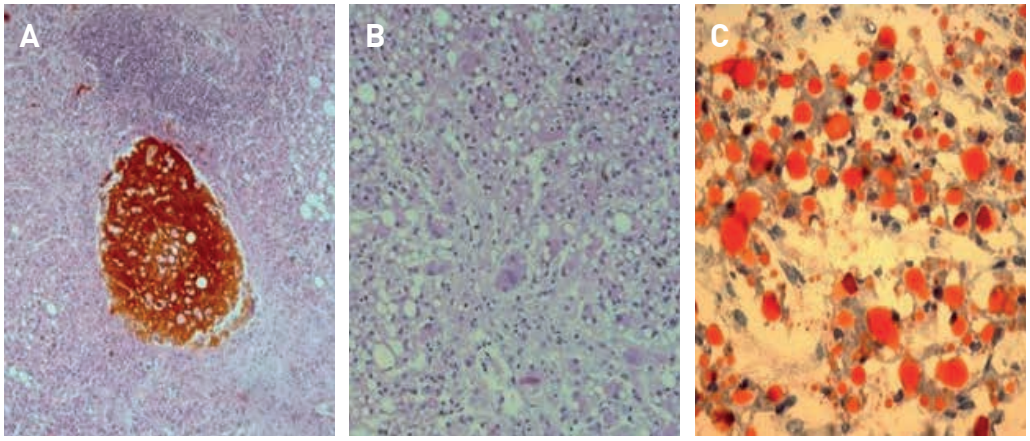


Figure 2.
Histological examination of the liver.

A – The portal tracts are expanded due to diffuse focal lymphoplasmacytic infiltration. Hepatocytes with signs of balloon dystrophy. There are sharply dilated bile ducts filled with bile. Hepatocytes of the periportal zone are in a state of micro-and macro vesicular steatosis, the total percentage of steatosis is about 70%. *Staining - hematoxylinand eosin. Magnification ×100.* B – The architecture of the liver is impaired due to edema, focal necrosis of hepatocytes, macro- microdroplastic steatosis. Sinusoids contain single erythrocytes, lymphocytes, and plasmocytes. The central veins are anemic. *Staining - hematoxylin and eosin. Magnification×200.* C - Groups of hepatocytes are visible, filled with fatty vacuoles stained red by ahistochemical reaction. *Coloring of Sudan III. Magnification ×200.*

Case 2

Patient N., 62 years old, was admitted to the Syzganov National Scientific Center of Surgery in the Department of General Surgery for the diagnosis of IPMN of main duct of pancreas. The patient also has type 2 diabetes mellitus. The disease began in September 2021, when pain appeared in the epigastrium and right hypochondrium, general weakness and it ching of the skin. Since October 2021, symptoms of jaundice and a15 kg decrease in body weight have appeared. In October 2021, the patient was treated in a hospital, where the total bilirubin level was 223 mmol/l, and the level of the cancer marker CA 19-9 was 199 U/ml. She underwent percutaneous transhepatic biliary drainage under ultrasound control, after which the bilirubin level decreased to 78 mmol/l. (Table2)

Table 2.
Data of laboratory tests after surgery

	Day 52	Day 59	Day 64	Day 68	Day 69
Total bilirubin (normal level 4,00- 20,50 mmol/l)	40.90	101.40	153.10	184.00	192.40
Direct bilirubin (normal level 0.00-5.10 mmol/l)	22.00	58.50	39.40	143.20	154.50
Prothrombin index (normal level 80.00 - 110.00 %)	46.2	38.4	34.7	31.3	27.50
INR (normal level 0.85-1.40)	1.62	1.78	1.97	2.28	2.57
White blood cells (normal level 4.0-9.0 10^9/l)	11.39	16.70	17.30	13.00	6.20

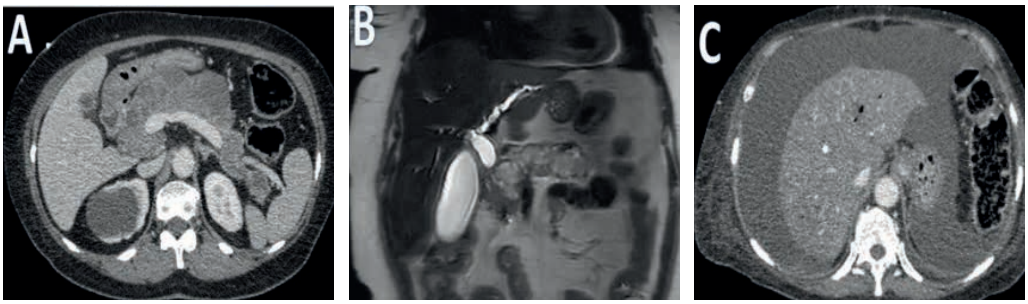
According to the results of contrast-enhanced computed tomography, the diagnosis of IPMN of the main pancreatic duct was established, with an increase in tumor size compared to the previous examination. After preparation, the patient underwent laparotomy and total pancreatoduodenectomy. Histologic examination revealed invasive intraductal mucinous papillary carcinoma of the pancreas. After surgery, the patient recovered without complications and was discharged after 14 days with an improvement in her condition.

In March 2022, the patient developed symptoms of abdominal enlargement, leg swelling, weakness, vomiting, and diarrhea. The patient was readmitted to the clinic with a diagnosis of malabsorption syndrome and protein-energy deficiency, as well as signs of ascites. Blood tests revealed hypoalbuminemia and marked electrolyte abnormalities. The patient underwent paracentesis and was prescribed albumin therapy.

On postoperative day 48, tests showed signs of severe coagulopathy, and total and direct bilirubin levels in the blood began to rise. The patient's general condition deteriorated. As a result, the patient was transferred to the Department of Anesthesiology and Intensive Care for further treatment.

Contrast-enhanced computed tomography of the abdominal cavity revealed hepatic atrophy with marked fat accumulation and massive ascites (Figure 3). The patient's clinical condition continued to deteriorate, and she developed severe liver failure with progressive hyperbilirubinemia. She died of FLD on the 69th day after surgery.

Figure 3.
Data of liver CT examination



A - Preoperative computed tomography of the abdominal cavity with signs of IPMN of the main duct of the pancreas. B - Magnetic resonance imaging of the liver shows signs of IPMN of the main duct of the pancreas. C - Postoperative computed tomography showed signs of pronounced fatty liver disease with atrophy, signs of liver failure, a decrease in liver parenchyma densityof+5+11 HU units and the presence of ascites. 59th day after surgery.

Discussion

These clinical cases represent a significant problem in the management of patients who have undergone pancreatic surgery, particularly in relation to the development of life-threatening FLD, which can develop within a short time after surgery. One of the characteristic features of this case was a significant loss of body weight due to malnutrition caused by surgery.

The most common patients with FLD have a number of risk factors, such as obesity, type 2 diabetes mellitus, dyslipidemia, and hypertension, which makes FLD a manifestation of metabolic syndrome.[23] However, in recent years, it has been noted that pancreatic surgery may also play a role in the development of FLD.[3,24,25] According to the latest data, the prevalence of this type of liver disease ranges from 23 to 37% among such patients.[3,25] *Sato T, et al. reported that the main risk factor for the development of FLD in such patients is pancreatic head cancer*.[3] At the same time, *Javed, A et.al.* identified five risk factors that may contribute to the development of FLD after pancreatic surgery: pancreatic adenocarcinoma, cancer in the resection area, pancreatic consistency, postoperative diarrhea, and eating disorders.[26]

The exact mechanisms leading to the development of FLD after PD are not fully understood. In contrast to the classical form of the disease, this form is not associated with obesity, hyperlipidemia, or insulin resistance.[3] A key role in the pathogenesis is played by EPI caused by its reduction in size after surgery, as well as nutritional disturbances leading to impaired absorption of essential amino acids, fats, and fat-soluble vitamins (e.g., choline). This is due to impaired synthesis of low-density lipoproteins in the liver and deficiencies of methionine and choline.[3,25-27] The use of high-dose pancreatic enzyme replacement therapy in patients with FLD after Parkinson's disease has shown a beneficial effect, supporting the proposed hypothesis about the pathogenesis of the disease.[3,26]

One possible mechanism is that a nutritional deficiency caused by a decrease in the exocrine function of the pancreas may contribute to the conversion of carbohydrates into fats in the liver. The key factors are neurogenic diarrhea associated with dissection of the nerve plexus around the superior mesenteric artery, impaired fat absorption, and steatorrhea caused by decreased exocrine activity of the pancreas. This impaired fat absorption is thought to contribute to an increase in the conversion of carbohydrates to fats in the liver.[28]

Another possible mechanism suggests that endotoxins may cause liver damage. A decrease in the exocrine function of the intestine may result in the movement of bacteria due to atrophy of the intestinal mucosa. This in turn may promote the entry of endotoxins into the liver through the portal vein, which activates Kupffer cells and causes steatosis in the liver.[29] It has also been hypothesized that this mechanism may be related to zinc deficiency. After extensive resection of the pancreas, there is a significant decrease in the blood level of zinc and its content in the pancreatic tissue. Zinc is mainly absorbed in the duodenum and proximal jejunum with the help of zinc-binding proteins in the pancreatic juice and plays an important role in the regeneration and maintenance of the epithelial structure of the intestinal mucosa. In addition to the restoration of part of the gastrointestinal tract after Parkinson's disease, the amount of zinc ingested from food also decreases due to a decrease in overall exocrine function. In addition, the hypofunction of insulin after PD increases the excretion of zinc in the urine, resulting in a deficiency of this trace mineral. It is believed that this reduces the protective role of zinc on the intestinal mucosa, which increases intestinal permeability and promotes the penetration of endotoxins through the mucosa.[30]

In these clinical cases, we did not measure serum zinc levels in these patients because they received parenteral nutrition containing zinc and magnesium immediately after surgery. Fatty liver hepatosis, which has developed in the context of protein and energy deficiency with severe liver failure, may be fatal in some cases.

Future recommendations should focus on the study of specific methods of perioperative nutrition, including caloric calculation and the use of nutritional supplements, taking into account the dynamics of weight changes and progression or improvement of liver steatosis. Our clinical cases indicate that following dietary recommendations in the postoperative period to maintain them with insulin therapy may play an important role in preventing a decrease in BMI in patients undergoing pancreatectomy.

Limitations. In these clinical cases, we did not measure serum zinc levels in these patients because they received parenteral nutrition containing zinc and magnesium immediately after surgery. Future recommendations should focus on studying specific methods of perioperative nutrition, including caloric calculation and use of nutritional supplements, taking into account the dynamics of weight changes and progression or improvement of liver steatosis.

What's known? These clinical cases represent a significant problem in the management of patients who have undergone pancreatic surgery, particularly in relation to the development of life-threatening FLD, which can develop in a short time after surgery. One of the hallmarks of this case was significant weight loss due to malnutrition caused by surgery.

What's new? There is a hypothesis that this mechanism may be related to zinc deficiency. After extensive resection of the pancreas, there is a significant decrease in the level of zinc in the blood and its content in the pancreatic tissue. After PD, the amount of zinc ingested from food also decreases due to a decrease in overall exocrine function. It is believed that this reduces the protective role of zinc on the intestinal mucosa, which increases intestinal permeability and promotes the penetration of endotoxins through the mucosa.

Conclusion

This clinical case demonstrates that life-threatening FLD with severe fibrosis can occur after PD and total pancreatectomy. When treating patients who have undergone pancreatic head resection or total pancreatectomy, physicians should consider the likelihood of developing fat-

ty liver and the importance of assessing nutritional status. It is necessary to use preventive drugs with pancreatic enzymes and supplements.

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