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CASE REPORT

Elevation of Pancreatic Enzymes in Gallbladder Bile Associated with Heterotopic Pancreas. A Case Report and Review of the Literature

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ABSTRACT

Context This is the first report associating heterotopic pancreas in the gallbladder and elevated pancreatic enzymes in bile. **Case report** A 60-year-old woman underwent abdominal ultrasonography at a medical check-up, revealing a nodular protrusion at the neck of the gallbladder. It seemed likely to be a lymph node, but we could not exclude the possibility of gallbladder cancer. In order to make a correct diagnosis, laparoscopic cholecystectomy was successfully performed. Pathological examination revealed heterotopic pancreatic tissue in the gallbladder wall. In addition, we detected elevated levels of amylase and lipase in gallbladder bile. **Conclusions** Preoperative diagnosis of heterotopic pancreas in the gallbladder is difficult. However, an increase of pancreatic enzymes in gallbladder bile may potentially play an important role in the occurrence of acalculous cholecystitis and biliary cancer. We need more accumulation of cases to know the true significance of this anomaly.

INTRODUCTION

Heterotopic pancreas is defined as tissue that is histologically similar to normal pancreas but appearing at an extra-pancreatic site and showing no anatomical or vascular connection with the original pancreas. Common sites of involvement include the upper gastrointestinal tract, such as the stomach, duodenum, proximal jejunum, and Meckel's diverticulum [1]. The clinical significance of heterotopic pancreas of the gallbladder, a relatively rare abnormality, is unclear. This report describes the findings regarding an asymptomatic patient presenting with heterotopic pancreas in the neck of the gallbladder. We demonstrated elevated levels of amylase and lipase in gallbladder bile of a patient with heterotopic pancreas for the first time in the world. This case suggests the existence of a potential relationship between heterotopic pancreas and biliary tract disease. It might be possible that we predict the future risk of biliary tract disease of such patients by measuring pancreatic enzymes in bile. However, we need more accumulation of cases to prove the true significance of the pathological condition.

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Key words Acalculous Cholecystitis; Biliary Tract Neoplasms; Cholecystectomy, Laparoscopic

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CASE REPORT

A 60-year-old woman presenting with no symptoms and no history of biliary colic underwent routine abdominal ultrasonography (US) as part of a medical check-up. The US results revealed a nodular protrusion sized 15 mm at the neck of the gallbladder (Figure 1). Despite this abnormality, the patient's abdomen was unremarkable on physical examination. Neither the results of routine blood tests, which revealed serum carcinoembryonic antigen concentration (CEA) and CA 19-9 levels within normal ranges, nor magnetic resonance cholangiopancreatography (Figure 2), which detected no pancreaticobiliary maljunction, indicated any other abnormality. Although the nodular protrusion seemed likely to be a lymph node, gallbladder cancer could not be ruled out because it was a wide-based protrusion. To determine whether the protrusion was

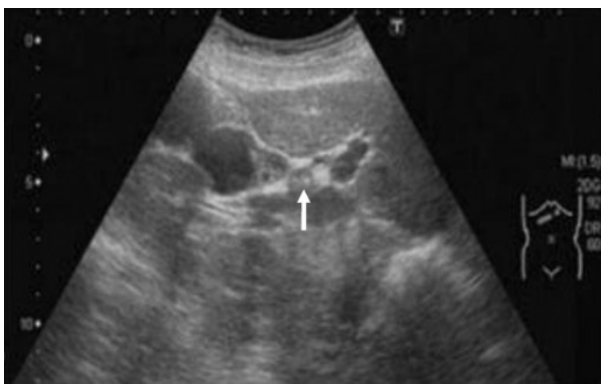

Figure 1. Abdominal ultrasound showing thickened lesion on neck of gallbladder (arrow).

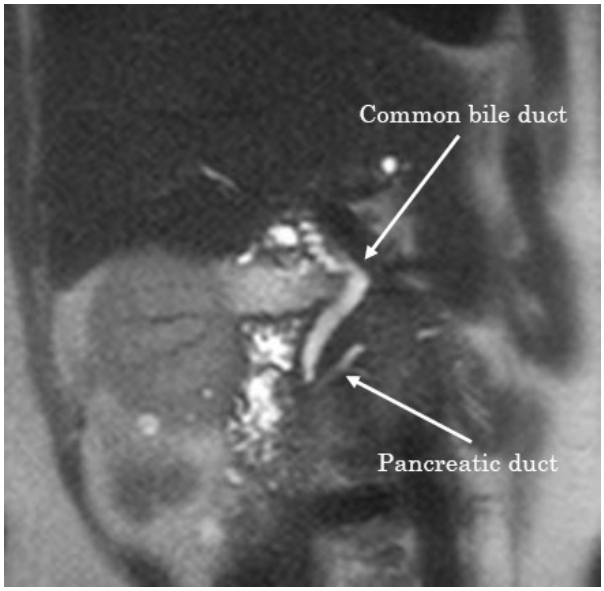

Figure 2. Magnetic resonance cholangiopancreatography revealing absence of pancreaticobiliary maljunction.

cancerous, laparoscopic cholecystectomy was performed using the standard 4-port technique for diagnosis and treatment. The intraoperative findings indicated that the protrusion was likely not cancerous. The postoperative course was uneventful and the patient discharged on the fourth postoperative day without any complications.

Macroscopically, diffuse thickening of the gallbladder wall and nodular thickening (7 mm in diameter) was observed near the cystic duct (Figure 3a). Histopathological examination revealed pancreatic acini and ducts without islets of Langerhans inside the nodular lesion and diffuse hyperplastic cholecystopathy (Figure 3bc). Based on these findings, the case was histologically diagnosed as adenomyomatosis and heterotopic pancreas in the gallbladder wall. We routinely measured the constituent of the bile in the resected gallbladder. We detected elevated amylase and lipase levels of 6,372 IU/L and 9,144 IU/L, respectively, compared to median levels of 24 IU/L and 246 IU/L, respectively, at the presenting in our hospital. For reference, the mean levels of amylase and lipase in bile in patients with pancreaticobiliary maljunction are 127,901 IU/L and 222,692 IU/L, respectively, in our hospital.

DISCUSSION

Heterotopic pancreas is a congenital anomaly characterized by growth of aberrant tissue mimicking normal pancreas without ductal or vascular continuity to the original gland. Heterotopic pancreas has traditionally been presumed to result from an error during embryological development, and is often only detected incidentally on laparotomy or autopsy. A recent theory contends that abnormalities in the Notch signaling system, specifically abnormalities in hairy and enhancer of split-1 (Hes-1), a main effector of Notch signaling required for lesion-appropriate pancreatic differentiation in the developing foregut endoderm [2], lead to development of heterotopic pancreatic tissue. The incidence of heterotopic pancreas has been reported to range from 0.55% to 13.7% at autopsy [2], but the true incidence is not known because most patients are asymptomatic. Common sites of involvement include the upper gastrointestinal tract, such as the stomach, duodenum, and proximal jejunum. Although heterotopic pancreas in the gallbladder is uncommon, pancreatic heterotopias causing acute and chronic cholecystopathy, gallbladder neck obstruction, and gallbladder perforation have been reported [3, 4, 5].

We reviewed 18 available cases of heterotopic pancreas of the gallbladder reported in the English literature (Table 1) [1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16]. Preoperative diagnoses could only be made for 13 cases, with 10 diagnosed as gallstones, two as polyps,

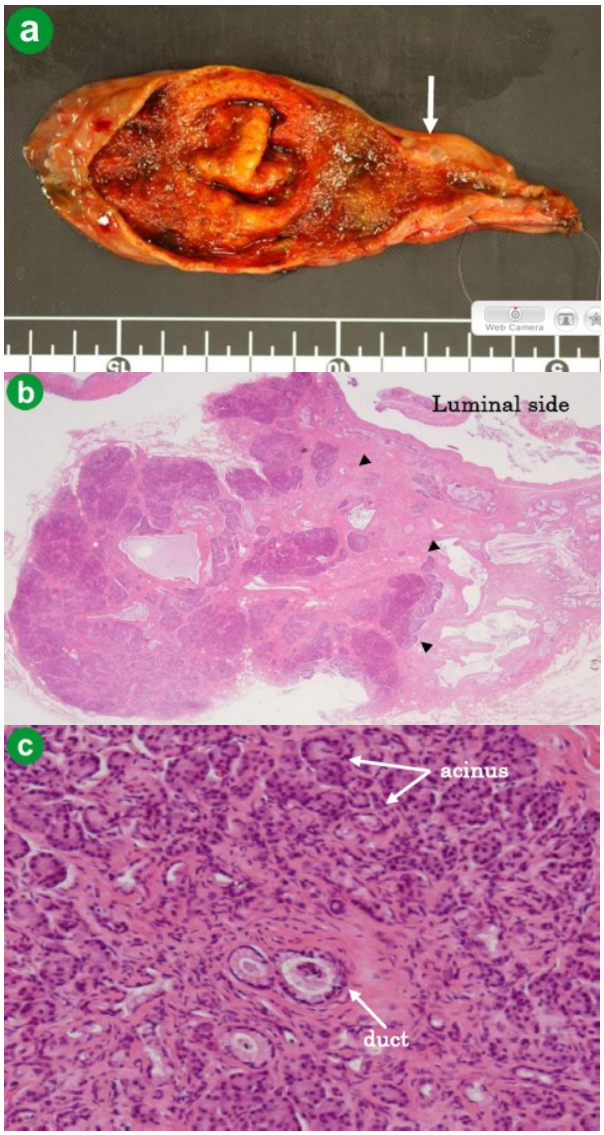

Figure 3. Image of protruding lesion near the cystic duct (**a.** arrow). The microscopy reveals pancreatic acinar and duct content in the layer of subserosa (**b.** H&E, x100; **c.** H&E, x400).

Table 1. Reported cases of heterotopic pancreas in the gallbladder.

Case	Author	Age (years)	Sex	Preoperative diagnosis	Location in gallbladder	Diameter	Von Heinrich's classification [17]	Symptomatic	Gallbladder stone
#1	Beltran *et al*. [1]	8	Male	GBS	Body	4 mm	I	+	+
#2	Beltran *et al*. [1]	22	Female	GBS	Neck	5 mm	I	+	+
#3	Shiwani *et al*. [3]	20	Female	GBS	Unknown	Unknown	I	+	+
#4	Ben-Brauch *et al*. [4]	45	Male	GBS	Neck	10 mm	I	+	+
#5	Mrak *et al*. [5]	75	Female	GBS	Neck	5 mm	I	+	+
#6	Weppner *et al*. [6]	26	Female	GBS	Neck	10 mm	I	+	-
#7	Elpek *et al*. [7]	40	Male	Unknown	Neck	9 mm	I	+	-
#8	Meshikhes *et al*. [8]	23	Female	GBS	Fundus	10 mm	I	+	+
#9	Mboti *et al*. [9]	23	Female	GBS	Unknown	Unknown	I	+	-
#10	Bhana *et al*. [10]	47	Female	Unknown	Neck	20 mm	I	+	-
#11	Murakami *et al*. [11]	49	Female	Polyp	Unknown	5 mm	II	-	-
#12	Kondi-Paphiti *et al*. [12]	58	Female	Polyp	Unknown	20 mm	I	+	-
#13	Kondi-Paphiti *et al*.[12]	48	Female	GBS	Unknown	15 mm	I	+	+
#14	Kondi-Paphiti *et al*. [12]	53	Female	Cancer	Unknown	20 mm	I	+	+
#15	Inceoglu *et al*. [13]	55	Female	GBS	Neck	13 mm	II	+	+
#17	Qizilbash [14]	54	Male	Unknown	Unknown	5 mm	I	+	-
#18	Elfving [15]	59	Female	Unknown	Unknown	Unknown	I	+	+
#19	Vidgoff *et al*. [16]	52	Male	Unknown	Unknown	10 mm	I	+	-

I: acinus, ducts and the islet of Langerhans; II: acinus and ducts; III: acinus only (Von Heinrich's classification is defined by components of the heterotopic pancreatic tissue [17]).
GBS: gallbladder stone

and one as cancer, with the diagnoses of the remaining 5 being unclear. Symptoms associated with cholecystitis were observed for 7 cases, but no gallstones were detected for these cases. The diameter of the heterotopic pancreas lesion of the 18 cases ranged from 4 to 20 mm (mean: 11 mm). In 15 cases, full components of pancreas, such as acini, ducts, and islets of Langerhans, were detected by histological examination of the resected specimen. None of the reports measured the concentration of pancreatic enzymes in the gallbladder bile.

The elevated levels of gallbladder bile amylase and lipase concentration observed in this study indicate that heterotopic pancreas tissue plays a role in exocrine functioning. As such, it is possible that the exocrine activity of heterotopic pancreas could cause pain and lead to the onset of acalculous cholecystitis. Furthermore, as does the pathophysiology resulting from pancreaticobiliary maljunction, elevation of pancreatic enzymes could eventually damage the biliary tract and gallbladder mucosa, leading to the development of gallbladder cancer. We consider that moderate elevation of pancreatic enzymes in gallbladder bile may be the feature in patients with heterotopic pancreas locating at gallbladder, as compared with the value of patients with pancreaticobiliary maljunction.

Generally, preoperative diagnosis of heterotopic pancreas in the gallbladder is difficult because of its rarity, leading this diagnosis to be unlikely to be considered in differential diagnosis. It is distant to make correct diagnosis for heterotopic pancreas preoperatively at present. However, we considered that measuring pancreatic enzymes in bile of the resected gallbladder might be useful for prediction of future risk of biliary cancer.

In conclusion, observation of an association between heterotopic pancreas in the gallbladder and elevated levels of pancreatic enzymes in bile (reported for the first time in this study) suggests the existence of a relationship between heterotopic pancreas and biliary disorders. Further research and examination of similar cases is required for confirmation of this relationship and further assessment of the clinical significance of heterotopic pancreas.

Conflicts of interest The authors have no potential conflicts of interest

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