[Case Report]

Hepatic Cyst Infection Following Recurrent Biliary Obstruction in Polycystic Liver Disease

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Abstract **:** An 89-year-old man with polycystic liver disease (PCLD) received uncovered self-expandable metallic stent (SEMS) placement above the papilla for malignant biliary obstruction caused by cholangiocarcinoma. He developed cholangitis ten months later due to SEMS occlusion caused by tumor ingrowth, and 2 plastic biliary stents were placed inside the SEMS across the papilla. Fever and right costal pain appeared two weeks after reintervention. Suspecting hepatic cyst infection based on imaging studies, percutaneous transhepatic cyst drainage was performed. Increased inflammatory cells and the presence of pathogens in the cyst fluid led to a definitive diagnosis of hepatic cyst infection. Following drainage, the hepatic cyst shrank with resolution of the symptoms. SEMS occlusive-related cholangitis or retrograde infection due to duodenal-biliary reflux after reintervention was considered as the cause of the hepatic cyst infection. Careful clinical and imaging evaluation should be performed in patients with PCLD undergone biliary stenting, because cyst infection may occur following stent occlusion or subsequent biliary reintervention.

Keywords **:** hepatic cyst infection, polycystic liver disease, cholangitis, recurrent biliary obstruction.

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Introduction

Polycystic liver disease (PCLD) is a hereditary disease and is caused by abnormal formation of the intrahepatic bile ducts. The most frequent complications of PCLD are bleeding, followed by infection or rupture [1]. Cyst infection is a rare complication, but if untreated it can lead to sepsis and may even cause death [2]. Hepatic cyst infection can be caused by the spread of pathogens from infected foci in other organs to the hepatic cysts. Intra-abdominal infections such as appendicitis and diverticulitis, for example, as well as pyelonephritis or endocarditis can be the causes [3, 4]. Pathogens derived from biliary infections can also be transmitted to hepatic cysts, with cholangitis and post-biliary reconstruction being the most common causes [5]. Currently, transpapillary biliary stenting for obstructive jaundice due to unresectable malignant biliary obstruction has become the gold standard for biliary drainage due to its minimally invasive nature, and is widely used [6]. Therefore, it is not uncommon to place biliary stents in patients with hepatic cysts. Biliary stent occlusion or retrograde infection due to duodenal-biliary reflux may be a cause of cyst infection, but its frequency is unknown because there have been no coherent reports to date. Herein we report the

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case of a PCLD patient who developed cyst infection after a reintervention for stent occlusion following uncovered self-expandable metallic stent (SEMS) placement for cholangiocarcinoma.

Case Report

An 89-year-old man came to our department one year ago with a complaint of jaundice, and contrast-enhanced computed tomography (CECT) showed irregular wall thickening with contrast effect in the middle common bile duct (Figure 1A). The CECT also showed more than 15 cysts in both lobes of the liver, one of which was about 10cm in size (Figure 1B). Endoscopic retrograde cholangiography (ERC) showed obstruction of the middle common bile duct (Figure 1C), and a biopsy of that area revealed adenocarcinoma, leading to a diagnosis of malignant biliary obstruction caused by cholangiocarcinoma. The patient and his family did not wish to undergo surgical treatment or chemotherapy for the treatment of cholangiocarcinoma. We placed double uncovered SEMS (Niti-S Large Cell D-type 10mm×100mm) above the papilla by the partial stent-in-stent method (Figure 1D). The reason for this was the possibility of intramural extension of the cancer into the perihilar bile ducts, since the enhancement of the common hepatic duct wall was conspicuous on CECT at the time of initial examination, and the gross morphology of the tumor was classified as the nodular invasive type. We therefore performed stenting, including the perihilar bile duct, by the partial stent-in-stent method in order to avoid stent occlusion due to tumor overgrowth. Ten months after the SEMS placement, the patient developed cholangitis due to SEMS occlusion caused by tumor ingrowth, and 2 plastic biliary stents (7Fr Through & Pass Double-Pit stent and 7Fr Through & Pass Straight stent) were placed inside each SEMS across the papilla as

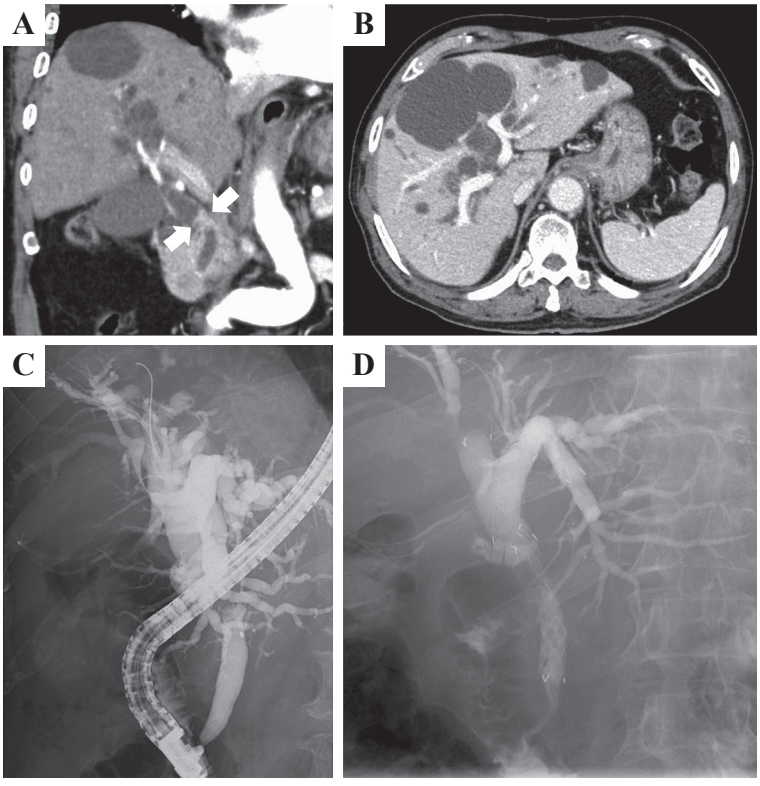

Figure 1. Computed tomography and endoscopic retrograde cholangiography images. A: Contrast-enhanced computed tomography image at the time of diagnosis of cholangiocarcinoma. Coronal image shows irregular wall thickening with contrast effect in the middle common bile duct (arrow). B: Axial image showing multiple hepatic cysts in both lobes of the liver, accompanied by intrahepatic bile ducts dilatation due to common bile duct obstruction. C: Endoscopic retrograde cholangiography showed stenosis of the middle common bile duct. D: Double uncovered self-expandable metallic stents (Niti-S Large Cell D-type 10mm×100mm) placed above the papilla by the partial stent-in-stent method.

biliary reintervention (Figure 2). Empiric antibiotics (tazobactam/piperacillin 4.5 g q8h) were administered intravenously for 5 days, and the patient's abnormal laboratory values, including hepatobiliary enzymes and inflammatory markers, began to improve the day after reintervention. Later, *Enterococcus species* were cultivated from the bile culture. On the 14th day after reintervention, the patient complained of fever and right costal pain. On physical examination, the patient had a fever of 38.5°C and tenderness in the right costal region. Laboratory data showed an elevated inflammatory response, and biliary enzymes elevated at the same level as before (Table 1). CECT showed a further increase in the size of the largest hepatic cyst previously recognized, and an increase in the density of surrounding mesenteric adipose tissue (Figure 3A, B). No obvious increase in density within the cyst could be recognized, and there was no contrast effect on the cyst wall (Figure 3B). Ultrasonography revealed mixed hypoechoic and hyperechoic areas within the cyst, and septum-like structures were recognized (Figure 3C).

Suspecting hepatic cyst infection, we performed percutaneous transhepatic cyst drainage. The drainage fluid was reddish brown, opaque, and contained many inflammatory cells, suggesting infection. The total bilirubin level in the cyst fluid was only 0.2 mg/d*l*. *Enterococcus species* were cultivated from the drainage fluid culture, which was the same pathogen as that cultivated in the bile culture obtained at the biliary reintervention. Cytology of the drainage fluid was performed several times, but no malignant cells were detected. After the drainage, the patient's right costal pain and inflammatory reaction gradually subsided; the cyst was also reduced in size on CT. Cystography through the drainage tube and cholangiography by ERC were performed to evaluate the communication between the cyst and bile ducts, and it was confirmed that there were no communications (Figure 4). Sclero-

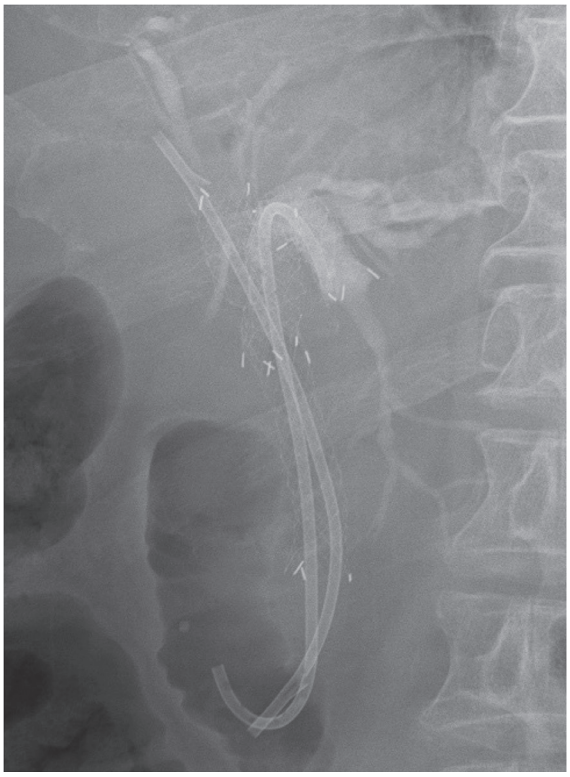

Figure 2. X-ray image at the time of reintervention. Placement of two plastic biliary stents (7Fr Through & Pass Double-Pit stent and 7Fr Through & Pass Straight stent) inside each self-expandable metallic stent as biliary reintervention.

Table 1. Laboratory data at the 14th day after reintervention.

Peripheral blood		Amylase	58 U/*l*
WBC	12,000 /μ*l*	CK	25 U/*l*
Eosinophil	0.0 %	BUN	13 mg/d*l*
Basophil	0.1 %	Creatinine	0.69 mg/d*l*
Lymphocyte	5.7 %	Glucose	105 mg/d*l*
Monocyte	2.7 %	HbA1c (NGSP)	5.4 %
Neutrophil	91.5 %		
RBC	365×10^4 /μ*l*	Serology	
Hemoglobin	11.5 g/d*l*	CRP	9.18 mg/d*l*
Platelet	14.8×10^4 /μ*l*		
		Coagulation	
Biochemistry		PT%	73.1 %
Total protein	5.7 g/d*l*	APTT	38.1 sec.
Albumin	2.6 g/d*l*	FDP	13.3 μg/m*l*
Total bilirubin	0.7 mg/d*l*	Fibrinogen	648 mg/d*l*
AST	30 U/*l*		
ALT	34 U/*l*	Tumor markers	
LDH	183 U/*l*	CEA	2.2 ng/m*l*
ALP	477 U/*l*	CA19-9	520 ng/m*l*
GGT	388 U/*l*		

WBC: white blood cell, RBC: red blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactic dehydrogenase, ALP: alkaline phosphatase, GGT: γ-glutamyl transpeptidase, CK: creatine kinase, BUN: blood urea nitrogen, HbA1c: hemoglobin A1c, CRP: C-reactive protein, PT%: prothrombin time%, APTT: activated partial thromboplastin time, FDP: fibrinogen degradation products, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9

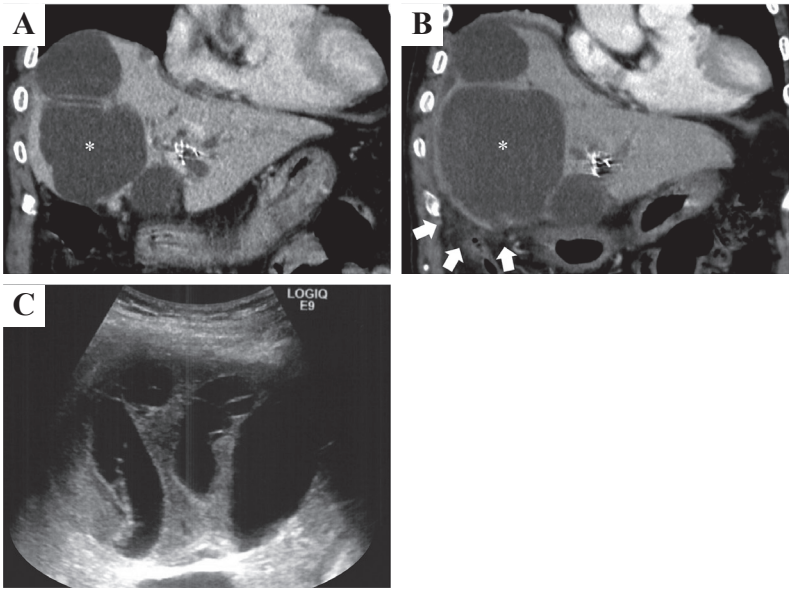

Figure 3. Computed tomography and ultrasonography images at diagnosis of hepatic cyst infection. A: Contrast-enhanced computed tomography (CECT) image one month prior to the onset of hepatic cyst infection. B: CECT image at diagnosis of hepatic cyst infection. The diameter of the hepatic cyst marked with an asterisk had increased from 10 cm to 12 cm. The area of increased density of mesenteric adipose tissue is indicated by arrows. C: Ultrasonography image showing mixed hypoechoic and hyperechoic areas within the cyst and recognition of septum-like structures.

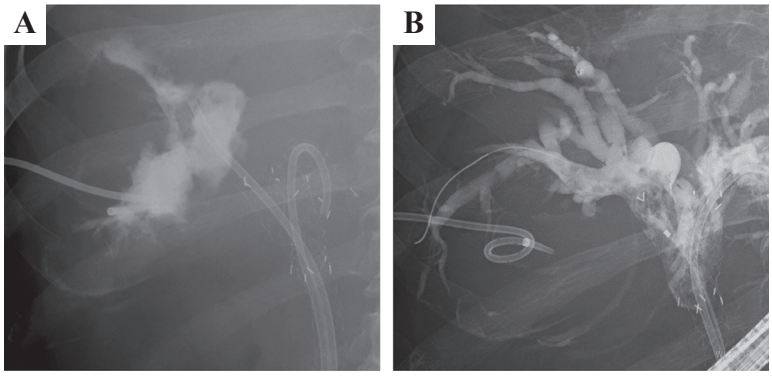

Figure 4. Cystography and endoscopic retrograde cholangiography images. A: Cystography through the drainage tube. B: Endoscopic retrograde cholangiography. No communications between the cyst and the bile ducts could be seen.

therapy for hepatic cyst was not performed because the patient was elderly and debilitated by the infection, and the drainage tube was not removed but was clamped. There was no recurrence of cyst infection thereafter, until his death from worsening cholangiocarcinoma.

Discussion

Multiple hepatic cysts can be divided into two groups: those that occur in association with autosomal dominant polycystic kidney disease, and those that are predominantly hepatic cysts with few or no renal cysts [7]. The Gigot classification, which is a severity classification of PCLD, divides hepatic cysts into 3 types according to the number, size and distribution [8]. In this case, there were less than five renal cysts in both kidneys and more than 15 cysts in the liver, one of which was about 10cm, corresponding to type I in the Gigot classification.

The complications of PCLD are divided into two categories: intra-cystic complications and liver volume-related complications [1]. Cyst infection, one of the intra-cystic complications, occurs in 1% of all pa-

tients with liver cysts [9]. Symptoms of hepatic cyst infection include right costal pain and fever, as in our case, but it is sometimes difficult to diagnose based on the symptoms, because some patients have fever alone [10]. Ultrasonography findings that trigger suspicion of cyst infection include the presence of intra-cystic sludge echoes [11]. CT shows increased density within the cyst and cyst wall thickness with contrast effect, while magnetic resonance imaging (MRI) shows decreased intensity within the cyst on T2-weighted images and abnormal signal on diffusion-weighted images [11]. Imaging techniques can be useful tools in the diagnosis of hepatic cyst infection, but ultrasonography and CT are negative in about 40% of scans performed in cases with a confirmed diagnosis [11]. It is important, therefore, to evaluate the cyst with multiple imaging studies, not just one.

In the present case, CT did not show any noticeable increase in density within the cyst or contrast effect on the cyst wall. Because of the increased cyst size and increased mesenteric adipose tissue density around the cyst on CT and the septal structures within the cyst on US, we suspected cyst infection and performed cyst puncture, which revealed findings of a cystic infection, i.e., increased inflammatory cells and presence of pathogens, leading to the definitive diagnosis [11]. When a cyst with septal-like structures is seen on US, hydatid cysts must be differentiated [12], but hemorrhage can also cause septal-like structures due to intracystic blood clots [13]. In our case, the drainage fluid was reddish brown, suggesting that the septal-like structures were caused by hemorrhage in combination with infection.

The routes of bacterial entry into hepatic cysts include bile duct, portal vein, hematogenous transmission, direct entry from nearby infected foci, and trauma [5]. In our case, we concluded that biliary infection was the cause of the hepatic cyst infection because there were no infected foci other than the biliary tract on imaging examination, and *Enterococcus species* were cultivated in both bile cultures at the time of the placement of the biliary plastic stents and cyst drainage fluid culture. The lack of elevation of bilirubin level in the cyst fluid and no communications between the cyst and bile ducts suggested that the route of infection could have been hematogenous transmission. Although isolation of the pathogen by blood culture was unsuccessful, the detection rate in blood culture is not high in hepatic cyst infection, reported to be about 60% [11]. Therefore, blood culture-negative does not rule out hematogenous transmission.

There are two possible triggers for the hepatic cyst infection in our case: the occurrence of cholangitis due to SEMS obstruction, or retrograde infection due to duodenal-biliary reflux after plastic stent placement as reintervention. It is also possible that the increased intrabiliary pressure caused by the SEMS occlusion may have caused a temporary communication between the cyst and bile ducts, resulting in cystic infection. In that hypothesis, however, cyst infection and cholangitis develop simultaneously, which is not consistent with the clinical course of the present case.

According to a report of hepatic cyst infection caused by cholangitis associated with bile duct stone, the time from the onset of cholangitis to the manifestation of cystic infection is 4 days [5]. In the present case, 2 weeks elapsed between the onset of SEMS occlusion-related cholangitis and the manifestation of cyst infection. The fact that the patient had been receiving antimicrobials for 5 days after the onset of cholangitis may have delayed the manifestation of the cyst infection. On the other hand, the biliary drainage for SEMS occlusion was plastic stent placement across the papilla, so duodenal-biliary reflux may have caused the cyst infection.

Although a rare occurrence, several cases of hepatic cyst infection have been reported in patients undergoing biliary reconstruction following pancreatoduodenectomy or liver transplantation [14, 15]. Loss of the anti-reflux function of the duodenal papilla has been proposed as the cause. Therefore, in the present case, endoscopic nasobiliary drainage tube placement should have been selected first to prevent duodenal-biliary reflux, followed by additional SEMS placement above the papilla in the form of stent-in-stent after improvement of cholangitis.

The pathogenesis of PCLD has been suggested to be associated with angiogenic mechanisms [16–18]. In PCLD, the expression of vascular endothelial growth factor (VEGF) and angiopoietin-1 (Ang-1) is strongly upregulated in cholangiocytes that comprise the cyst epithelium [16]. VEGF and Ang-1 act autocrinally

on cholangiocyte proliferation and paracrine on portal vasculature to promote cyst growth and its vascular supply [16]. In enlarged cysts, the development of vasculature may provide an environment conductive to the hematogenous transfer of bacteria into the cysts. This may account for the fact that only the largest cyst was infected, even though there were multiple hepatic cysts in our case.

In summary, we experienced PCLD complicated by hepatic cyst infection after biliary plastic stent placement across the papilla for SEMS occlusion. Careful clinical and imaging evaluation should be performed in patients with PCLD undergone biliary stenting, because cyst infection may occur following stent occlusion or subsequent biliary reintervention. It is also important to select a reintervention strategy that takes into account the risk of cyst infection due to duodenal-biliary reflux when reintervention is required.

Conflict of Interest

The authors declare that there is no conflict of interest.

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