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CASE REPORT

Biliary tuberculosis causing cicatricial stenosis after oral anti-tuberculosis therapy

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Abstract

A 36-year-old Philippine woman presented with dark urine and yellow sclera. Endoscopic retrograde cholangiopancreatography (ERCP) confirmed dilatation of the intrahepatic bile ducts and also showed an irregular stricture of the common hepatic duct at the liver hilum. Histological examination of biopsies from the bile duct revealed epithelioid cell granulomas and caseous necrosis. Tubercle bacilli were then detected on polymerase chain reaction (PCR) testing of the bile, giving the diagnosis of biliary tuberculosis. Although microbiological cure was confirmed, the patient developed cicatricial stenosis of the hepatic duct. She underwent repeated treatments with endoscopic biliary drainage (EBD) tubes and percutaneous transhepatic biliary drainage (PTBD) tubes, and the stenosis was corrected after 6 years. We present a case of tuberculous biliary stricture, a condition that requires careful differentiation from the more common malignancies and needs long-term follow-up due to the risk of post-treatment cicatricial stenosis, although it is rare.

Key words: Biliary tuberculosis; Obstructive jaundice; Cicatricial stenosis; Polymerase chain reaction

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INTRODUCTION

The more common benign causes of biliary stenosis are postoperative cicatricial stenosis and complications of chronic pancreatitis, duodenal papillitis, and congenital biliary dilatation, whereas tuberculous lesions, such as tuberculosis (TB) of the biliary lymph nodes, pancreatic TB, and biliary TB are rare. In this paper, we report a case of biliary TB causing obstructive jaundice and cicatricial stenosis after oral anti-tuberculosis therapy.

CASE REPORT

The patient was a 33-year-old female of Philippine origin. She presented with dark urine, yellow sclera, and malaise. She had lived in Japan for 3 years when she was admitted to our hospital. Her father and brother had a past history of pulmonary TB. She received no past treatment for TB. When she visited a local doctor in May 1998 for symptoms of dark urine and yellow sclera, she was found to have mild hepatic dysfunction and was thus referred to our hospital with suspected acute hepatitis. Viral, drug-induced, and auto-immune hepatitis were excluded, and she was treated with watchful anticipation as an outpatient. Abdominal ultrasound then revealed dilatation of the intrahepatic bile ducts and multiple intrahepatic hypodense areas, and the patient was admitted to our hospital for further investigation in February 1999. Admission findings included: height 154 cm, weight 54 kg, and body temperature 36.4℃. Her blood pressure was 112/62 mmHg, heart rate was 64 beats/min, and she had a sinus rhythm. Conjunctiva was not anemic or jaundiced. No superficial lymph nodes were palpable. Abdomen was flat and soft. The liver, spleen or masses were not palpable without abdominal pain or tenderness. Full blood examination revealed that she had mild anemia (117 mg/L; normal: 125-170 mg/L) and an elevated erythrocyte sedimentation rate (66 mm/h; normal: <10 mm/h). Serum biochemistry showed elevated biliary enzyme γ-glutamyltranspeptitase (201 IU/L; normal: 12-70 IU/L). Tumor markers CA19-9 (100 KU/L; normal: <37 KU/L) and PIVKA-II (43 AU/L; normal: <10 AU/L) were elevated. Abdominal ultrasonography (US) showed the hepatic parenchyma to be uniform and slightly hypertrophic, with dilatation of the intrahepatic ducts and multiple hypoechoic masses (Figures 1A and B). Abdominal computed tomography (CT) scans confirmed intrahepatic ductal dilatation and multiple hypodense lesions in the liver, some with micro-calcifications. The early contrast phase images showed slight enhancement of the periphery of the lesions, while the late phase images showed uneven enhancement

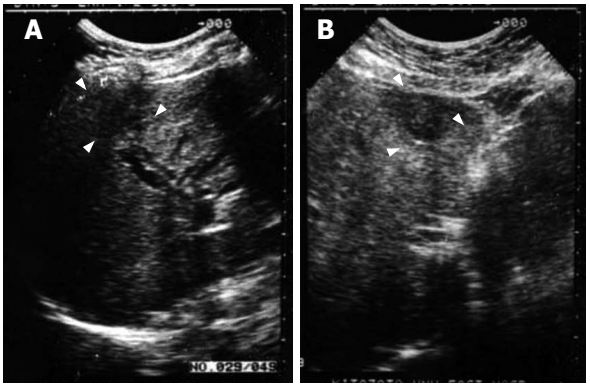

Figure 1 Ultrasonography findings of the liver. **A**: Dilatation of the intrahepatic ducts and a hypoechoic mass in the right lower anterior segment; **B**: A heterogeneous mass in the inner left segment.

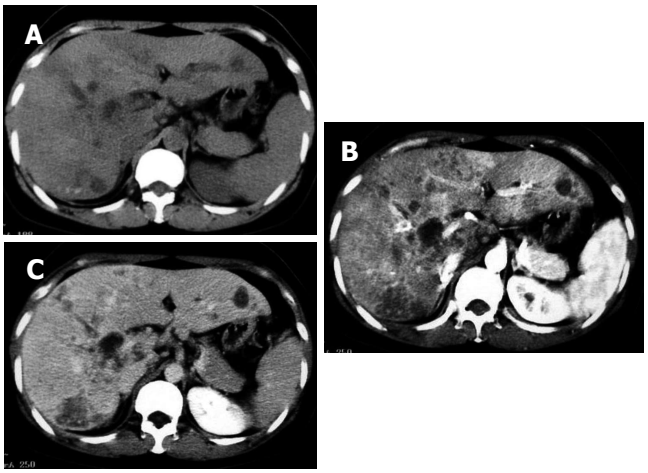

Figure 2 Abdominal computed tomography (CT). **A**: Plain CT images show intrahepatic ductal dilatation, micro-calcifications, and multiple hypodense lesions in the liver; **B**: Contrast CT image (early phase) shows clearly delineated hypodense lesions; **C**: Late phase CT image shows slightly enhanced hypodense lesions.

of the peripheral and central areas. Lymphadenopathy was seen both at the liver hilum and at the origin of the splenic artery (Figures 2A-C). Intraductal ultrasonography (IDUS) showed soft tissue masses at the liver hilum of the hepatic duct (Figure 3A), and circumferential thickening of the common hepatic duct (Figure 3B). Endoscopic retrograde cholangiopancreatography (ERCP) revealed that the common hepatic duct was narrowed over a 2 cm section, and the hepatic ducts were clumped and irregular at the liver hilum, with strictures of the feeding branches from each section of the liver (Figures 4A and B). Histopathological examination of endoscopic biopsy specimens from the common hepatic duct at the liver hilum revealed granulomas with epithelioid cells (Figure 5A), whereas a biopsy specimen from a hepatic mass showed very mild atrophy and marked dilatation of the hepatic sinuses, with large foci of caseous necrosis surrounded by epithelioid granuloma (Figure 5B). Repeated bile cytodiagnosis showed no malignancy. Cholangiography showed irregular strictures of the intra and extra hepatic biliary ducts. So hepatic secondaries from malignant neoplasia were mostly suspected, but the

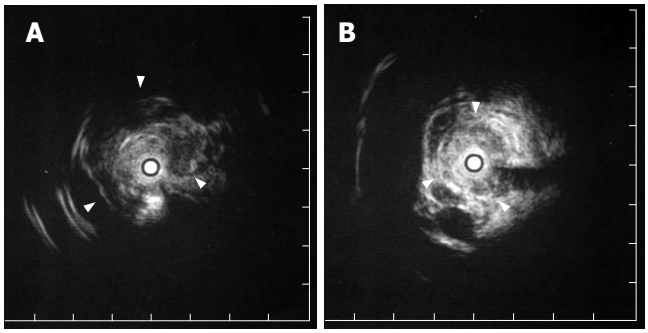

Figure 3 Endoscopic ultrasonography (EUS). **A**: Soft tissue masses at the liver hilum of the hepatic duct; **B**: Circumferential thickening of the common hepatic duct.

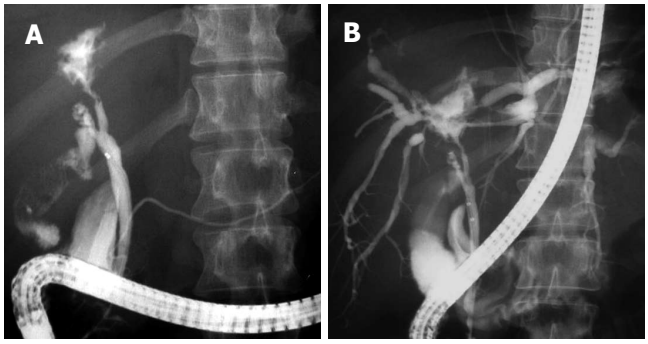

Figure 4 Endoscopic retrograde cholangiopancreatography examination. **A**: The common hepatic bile duct was narrowed over a 2 cm section, and strictures and irregularities of the hepatic bile duct at the liver hilum were revealed; **B**: The hepatic ducts at the liver hilum were clumped with strictures of the feeding branches from each section of the liver.

biopsies and bile cytodiagnosis did not show malignancy. Then the differential diagnosis could include primary biliary sclerosis (PSC), drug-induced cholestasis, and HIV-associated cholangiopathy. Serum ALP was normal with no obvious elevations in liver enzymes. Also serum anti-mitochondrial antibody and peripheral anti-neutrophil cytoplasmic antibody (pANCA), and smooth-muscle antibody did not elevate. Symptoms of inflammatory bowel disease, particularly ulcerative colitis did not present. She took no medicine and her serum HIV was negative. The biopsy findings of caseous necrosis and epithelioid granulomas, and bile polymerase chain reaction (PCR)-confirmed tubercle bacilli, led to the diagnosis of biliary TB. Tuberculin test was also strongly positive. Triple anti-tuberculosis therapy, comprising 400 mg isoniazid (INH) daily, 750 mg ethambutol (EB) daily, and 450 mg rifampicin (RIF) daily, was administered for 7 mo. Microbiological cure was confirmed in October 1999, with phlegm, gastric juice, bile, and feces negative for *Mycobacterium tuberculosis*. In December 2000, 14 mo after the completion of anti-tuberculosis treatment, the patient became febrile and jaundiced. Endoscopic retrograde cholangiography (ERC) demonstrated cicatricial stenosis of the common hepatic duct at the liver hilum. Because of the tight stricture at the liver hilum, and narrowing of many intrahepatic bile ducts, transpapillary stent placement was abandoned, and percutaneous transhepatic biliary drainage (PTBD) was performed instead (Figure 6A). Although she subsequently

Table 1 Summary of the 16 previous cases and our case of tubercular biliary stricture

No.	Age	Sex	Site of stricture	Initial presentation	Confirmation of diagnosis	Treatment	Outcome	Reference/Nation
1	30	M	CBD	CCC	Laparotomy frozen section	T-tube		Gupta *et al*[2]/India
2	78	F	Multiple	Bacterial cholangitis	Laparotomy frozen section	Laparoscopic cholecystectomy	Died of sepsis	Abascal *et al*[3]/Spain
3	46	F	CHD	CCC	Laparotomy frozen section	PTBD, surgical bypass was abandoned	Post anti-TB therapy, pulmonary calcification	Fan *et al*[4]/Hong Kong, China
4	38	M	CBD	CCC	Laparotomy frozen section	T-tube		Ratanarapee *et al*[5]/Thai
5	46	F	CHD		Bile cytology	EBD (Pl, metal)	Biliary stones, restenosis	Bearer *et al*[6]/USA
6	40	M	CBD	CCC	Laparotomy frozen section	Hepaticojejunostomy		Behera *et al*[7]/India
7	45	F	CBD	CCC	Laparotomy frozen section	Hepaticojejunostomy		Valeja *et al*[8]/India
8	70	M	CBD, CHD	CCC	Culture of biopsy of inguinal lymph node	ERBD (refused operation)	Post anti-TB therapy, pulmonary calcification	Hickey *et al*[9]/Ireland
9	46	M	CBD		CT guided FNAB	EBD	Restenosis	Kok *et al*[10]/Brunei
10	29	F	CHD, HD		Bile cytology	Left cholangiojejunostomy		Kok *et al*/Brunei
11	60	F	CBD	CCC	Laparotomy frozen section	Open billiary stenting		Kok *et al*/Brunei
12	44	F	CHD	CCC	Laparotomy frozen section	Hepaticojejunostomy	Hepatic calcification	Kok *et al*/Brunei
13	33	F	CHD	CCC	Laparotomy frozen section	Hepaticojejunostomy		Yea *et al*[11]/Taiwan, China
14	70	M	HD		PCR of bile	PTBD	Billroth II reconstruction	Yea *et al* /Taiwan, China
15	58	M	Multiple	CCC	Tissue obtained via PTBD	PTBD (metal)	Beaded type	Inal *et al*[12]/Turkey
16	66	M	CBD, RHD	CCC	Laparotomy frozen section	T-tube, PTCD	Post anti TB therapy	Prasad *et al*[13]/India
17	33	F	CHD		PCR of bile	PTBD, EBD	Pulmonary calcification, biliary stones, restenosis	Our case/Japan

CCC: Cholangio cell carcinoma; HD: Hepatic duct, RHD: Right hepatic duct; LHD: Left hepatic duct; CHD: Common hepatic duct; CBD: Common bile duct; FNAB: Fine-needle aspiration biopsy; ERCP: Endoscopic retrograde cholangiopancreatography; PTCD: Percutaneous transhepatic biliary drainage; EBD: Endoscopic biliary drainage.

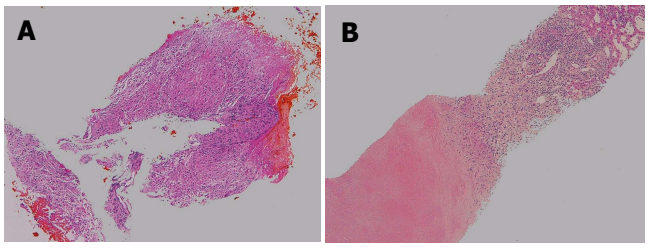

Figure 5 Histological findings of the biopsy specimen stained with HE. **A**: Photomicrograph of an endoscopic biopsy specimen from the common hepatic duct showing granulomas with epithelioid cells; **B**: Photomicrograph of a biopsy specimen from a hypoechoic mass in the liver showing focal caseous necrosis surrounded by granuloma.

experienced repeated bouts of pyrexia and jaundice due to ascending cholangitis, the stenosis improved gradually, and fistularisation was achieved in July 2001 (Figure 6B). By February 2003, only two 7 Fr pigtail catheters were required for endoscopic biliary drainage (EBD) tube placement (Figure 6C). Two years later (in January 2005), a further bout of cholangitis made the patient febrile but not jaundiced, and no stenoses were detected on ERC (Figure 6D), so the EBD tubes were removed. She developed biliary stones in April of the same year, which was not detected before. However, EBD tube was reinserted and follow-up was continued at the time of writing this paper.

DISCUSSION

Benign biliary strictures fall into two etiological groups: traumatic (post operative, blunt, or penetrating injury) and nontraumatic (sclerosing cholangitis, recurrent pyogenic cholangitis, chronic pancreatitis, Mirizzi syndrome). The site and number of strictures depend on the cause. TB is a rare cause of biliary obstruction. Hepatobiliary TB may be caused by three ways: spread of caseous material from the portal tracts into the bile ducts (most often), secondary inflammation-related tuberculous periportal adenitis, and spread of caseous material through the ampulla of Vater and ascending along the common bile duct. Hepatobiliary TB can be classified into 3 types: miliary hepatic TB, hepatic tuberculoma, and biliary TB[1]. The majority are the miliary TB type. Hepatic tuberculoma requiring differentiation from hepatoma is relatively rare. Biliary TB is even more uncommon, and no cases of biliary TB causing obstructive jaundice due to biliary stenosis have been reported in Japan. A Pub Med search of papers published after 1985 has yielded 16 reported cases of biliary TB causing obstructive jaundice[2-13] (Table 1). In each case, irregular stenosis of one or more bile ducts was seen on ERC, these findings differing considerably from those in cases of TB of the biliary lymph nodes or pancreatic TB, where obstructive jaundice is caused by extramural compression of the common bile duct (CBD). Differentiation from malignant neoplasia was often extremely difficult, and in 11 of the 16 cases laparotomy was performed without having excluded malignancy, and a preoperative diagnosis of TB was achieved through biopsy or PCR in only 5 cases. In 1 case, although the diagnosis of TB had been made, choledochoduodenostomy was required due to multiple strictures. 2 cases were complicated by biliary stones, and cicatricial restenosis occurred in the same cases following medical treatment. The bile duct might have been severely damaged by repeated inflammatory reactions and have become irreversibly scarred. One case had a postinflamamtory stricture for nearly 2 years[6] and one case required stent changes every 6 mo at the issue[10]. And only 2 cases were

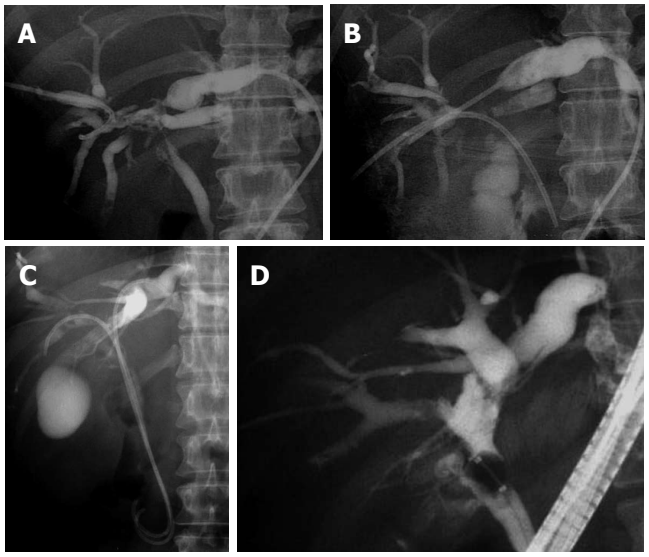

Figure 6 ERC following anti-tuberculosis therapy showing marked irregularity of the hepatic ducts and strictures of common hepatic duct. **A**: PTBD tubes were inserted via the B8 and B3 branches; **B**: The PTBD tube from the B5 branch was inserted into the common bile duct; **C**: EBD tubes were inserted into both hepatic lobes; **D**: The strictures of the hepatic duct s were recanalized.

with radiological evidence of pulmonary tuberculosis and one case with hepatic calcification, so TB must be considered in the differential diagnosis of any bile duct obstruction, particularly in patients from areas where TB is prevalent.

Biliary TB is a condition with no specific clinical findings and is usually diagnosed through biopsy or the detection of tubercle bacilli. The detection rate through culture is 0%-10%[14]. However, even if epithelioid granulomas are identified, differentiation from conditions such as hepatic sarcoidosis or inflammatory bowel disease is important. Sarcoid granulomas are similar to TB granulomas, although in the former foreign body-type giant cells are seen in addition to Langhans giant cells, and foci of necrosis are rarely seen. In this case, acid-fast bacilli were not detected by culture or microscopy, and *Mycobacterium tuberculosis* was only detected through PCR testing of the bile. Since PCR testing for *Mycobacterium tuberculosis* is extremely sensitive, it should be used extensively. Although favourable results can be achieved by medical therapy with repeated stenting of the bile ducts, long-term follow-up is required due to the risk of post-treatment cicatricial stenosis.

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