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.

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°C. 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-glutamyltransferase (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.

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.

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

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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 strictures and irregularities of the hepatic bile duct at the liver hilum were revealed; the hepatic ducts at the liver hilum were clumped with strictures of the feeding branches from each section of the liver.

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 extrahepatic bile ducts. So hepatic secondaries from malignant neoplasia were mostly suspected, but the 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 antimitochondrial 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 antituberculosis 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 antituberculosis 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    | Died of sepsis | Gupta et al[2]/India |
| 2   | 78  | F   | Multiple          |Bacterial cholangitis | Laparotomy frozen section | Laparoscopic cholecystectomy | Post anti-TB therapy, pulmonary calcification | 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    | Biliary stones, restenosis | Ratanarapee et al[5]/Thai |
| 5   | 46  | F   | CBD               |Bile cytology         | EBD (PL, metal)           | Biliary stones, restenosis | Bearer et al[6]/USA |
| 6   | 40  | M   | CBD               |CCC                   | Laparotomy frozen section | Hepaticeojunostomy         | Behera et al[7]/India |
| 7   | 45  | F   | CBD               |CCC                   | Laparotomy frozen section | Hepaticeojunostomy         | 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 cholangioejunostomy | Kok et al[10]/Brunei        | Kok et al[10]/Brunei |
| 11  | 60  | F   | CBD               |CCC                   | Laparotomy frozen section | Open biliary stenting      | Kok et al[10]/Brunei        | Kok et al[10]/Brunei |
| 12  | 44  | F   | CHD               |CCC                   | Laparotomy frozen section | Hepaticeojunostomy         | Hepatic calcification      | Kok et al[10]/Brunei |
| 13  | 33  | F   | CBD               |CCC                   | Laparotomy frozen section | Hepaticeojunostomy         | Yea et al[11]/Taiwan, China | Yea et al[11]/Taiwan, China |
| 14  | 70  | M   | HD                |PCR of bile           | PTBD                      | Billroth II reconstruction | Inal et al[12]/Turkey       | Inal et al[12]/Turkey |
| 15  | 58  | M   | Multiple          |CCC                   | Tissue obtained via PTBD  | PTBD (metal)                | Post anti TB therapy       | Prasad et al[13]/India |
| 16  | 66  | M   | CBD, RHD          |CCC                   | Laparotomy frozen section | T-tube, PTCD               | Pulmonary calcification, biliary stones, restenosis | Our case/Japan |
| 17  | 33  | F   | CHD               |PCR of bile           | PTBD, EBD                 | Pulmonary calcification, biliary stones, restenosis | |

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

**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 perportal 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 tuberculosis, and biliary TB[11]. The majority are the miliary TB type. Hepatic tuberculosis 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 PubMed 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 cicatrical 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 postinflammatory stricture for nearly 2 years[6] and one case required stent changes every 6 mo at the issue[10]. And only 2 cases were...
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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