Letter to the Editor

Withered branch-like changes of intrahepatic bile ducts: a rare complication of acute severe biliary pancreatitis

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Secondary sclerosing cholangitis (SSC) is a chronic biliary disease characterized by inflammatory responses, fibrous occlusion, strictures, and progressive destruction of intrahepatic and/or extrahepatic bile ducts, which may lead to cholestasis and cirrhosis (1). Well-described causes of SSC include infectious, ischemic, toxic, immunologic, congenital disorders and so on (2,3). Here, we presented a rare case of sclerosing cholangitis secondary to acute severe biliary pancreatitis.

A 45-year-old woman with a medical history of hypertension and cholecystolithiasis presented suddenly with increasingly frequent episodes of right upper abdominal pain and jaundice, with normal liver function shown in regular annual examination two months before disease onset. She was referred to the local hospital several hours later as the symptoms aggravated quickly. Severe acute pancreatitis (SAP) was diagnosed and small stones in the common bile duct and gallbladder shown in magnetic resonance cholangiopancreatography (MRCP) and ultrasound indicated the biliary origin (*Figure 1A*, red arrow). Total/direct bilirubin levels showed 50.5/40.2 μmol/L, with alanine aminotransferase (ALT) 505 U/L, aspartate aminotransferase (AST) 286 U/L, alkaline phosphatase (ALP) 240 U/L and γ-glutamyl transferase (GGT) 945 U/L. He received mechanical ventilation and hemofiltration in the intensive care unit, as well as early nasal jejunal nutrition and other active conservative treatment. Multiple times of percutaneous drainage followed by minimally invasive necrosectomy were conducted (*Figure 1B*). Endoscopic retrograde cholangiopancreatography (ERCP) was not performed immediately concerning about the high risk of post-ERCP pancreatitis. Afterwards, she had an attack of cholecystitis, which was controlled by percutaneous transhepatic gallbladder drainage and antibiotics. Bilirubin levels subsequently fell down but kept at about 30.0/20.0 μmol/L. Oral feeding resumed 4 months after disease onset and the patient discharged with drainage tube.

However, she soon developed continuous high fever with positive blood cultures (*Klebsiella pneumoniae*), with total/direct bilirubin levels fluctuating at 50–60/40–45 μmol/L. Antibiotics were effective but could not be withdrawn entirely after full-course use. Multiple stones were removed from common bile ducts through ERCP 1 month after recurrent fever. The culture of nasobiliary drainage showed the same multi-drug resistant *Klebsiella pneumoniae* as blood cultures.

The patient was transferred to our hospital due to persistent jaundice and recurrent cholangitis. The general condition was weak and the body mass index was only 16 kg/m^2 on admission. Blood tests showed total/direct bilirubin levels showed 61.9/49.9 μmol/L, ALT 37 U/L, AST 58 U/L, GGT 458 U/L, ALP 919 U/L. MRCP showed withered branch-like change in the intrahepatic bile duct (*Figure 1C*), with positron emission tomography/

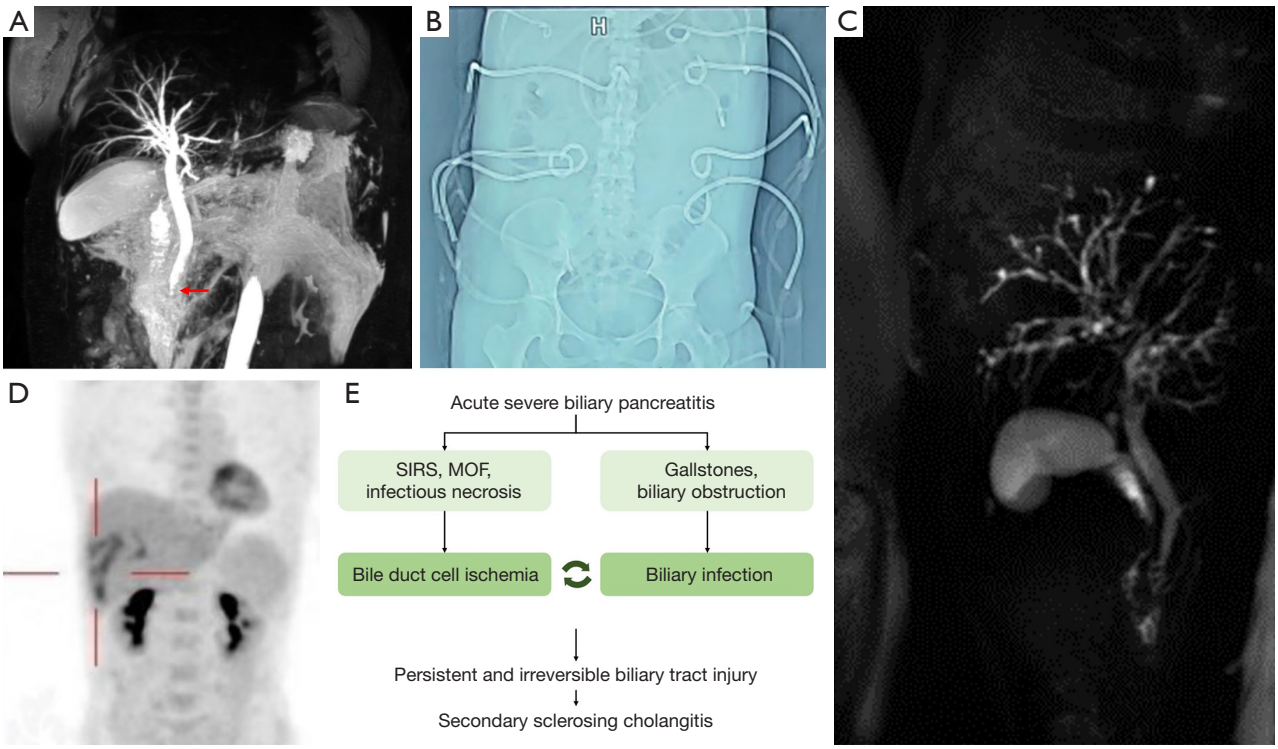

Figure 1 Development of sclerosing cholangitis after acute severe biliary pancreatitis. (A) MRCP at disease onset showed a small stone in the intrapancreatic segment of the common bile duct (red arrow) with normal-shaped intrahepatic bile duct. (B) Multiple times of percutaneous drainage for local complications of SAP. (C) MRCP nine months after disease onset indicated withered branch-like changes of intrahepatic bile duct. (D) PET/CT revealed a right liver-dominated hypermetabolic focus distributed along the intrahepatic bile duct (red target mark). (E) Potential mechanism of SSC in this case report. H, head; SIRS, systemic inflammatory response syndrome; MOF, multiple organ failure; MRCP, magnetic resonance cholangiopancreatography; SAP, severe acute pancreatitis; PET/CT, positron emission tomography/computed tomography; SSC, secondary sclerosing cholangitis.

computed tomography (PET/CT) suggesting infection sites distributed along the intrahepatic bile duct (*Figure 1D*). Hepatic cirrhosis was diagnosed based on the liver stiffness measurement of 10.0 kPa. Further serum screenings for tumors, autoantibodies, IgG4, blue copper protein, and hepatotropic virus were all negative. The patient refused liver biopsy.

The wither-like changes of intrahepatic bile ducts showed in MRCP were typically consistent with sclerosing cholangitis, and primary sclerosing cholangitis (PSC) was the primary differential diagnosis. However, MRCP at the onset of SAP did not show specific changes in the intrahepatic biliary duct and liver function was normal before disease onset, supporting the diagnosis of SSC. While considering alternative possibilities, autoimmune, neoplastic, congenital, viral, and other factors were also ruled out. Therefore, based on medical history, laboratory tests and radiology, SSC secondary to SAP and recurrent biliary infections were diagnosed, which suggested an irreversible changes in intrahepatic bile ducts.

Considering the high difficulty and risk of percutaneous transhepatic cholangial drainage (PTCD), the therapeutic preference for adequate antibiotics and strict nasal jejunal nutrition were promoted, as well as adequate ursodeoxycholic acid. The patient's symptoms improved with continuous application of broad-spectrum antibiotics and adequate nasal jejunal nutrition, and she gained weight slowly. Two months later, the patient resumed oral intake and discontinued antibiotics without fever. However, the total/direct bilirubin levels kept at 60–80/50–70 μmol/L, without improvement of wither-like changes in intrahepatic bile ducts. And liver transplantation might be considered if recurrent cholangitis or decompensated cirrhosis could not be avoided in the future.

This case explicitly presents the development of sclerosing cholangitis as a rare complication secondary to acute severe biliary pancreatitis. SSC is commonly diagnosed based on typical serological indicators of cholestasis and bead-like or wither-like changes of bile ducts in MRCP with definite secondary causes. Liver biopsy may be necessary for atypical conditions. The formation mechanism of SSC is multifactorial. According to previous studies, ischemia and 'toxic bile' are reported as underlying potential pathophysiological mechanisms of SSC (1). Up to now, there are few case reports about sclerosing cholangitis secondary to SAP and recurrent cholangitis (4). The potential mechanisms in this case may be speculated as follows: (I) systemic inflammatory response syndrome (SIRS), hypoperfusion, and organ dysfunction in the early phase of SAP might sacrifice the biliary blood supply. These processes resemble sclerosing cholangitis in critically ill patients, where severe hypotension, microcirculatory disturbances, and SIRS/sepsis are potential triggers (5). In the late phase of SAP, extensive pancreatic and peripancreatic necrosis may also disrupt the blood supply to the biliary system. (II) Simultaneously, the recurrent antibiotic-dependent biliary infection secondary to biliary dysfunction and delayed drainage methods (e.g., ERCP) also make things worse, which is supported by PET/CT. (III) A vicious cycle of ischemia and recurrent biliary infection may lead to persistent and irreversible intrahepatic sclerosing cholangitis (*Figure 1E*).

It is worthy noting that although the underlying cause of SSC is relatively well-defined, disease progression and prognosis are usually less controlled than those in PSC (2). Treatment options are usually limited and liver transplantation could be considered if the patient suffers from repeated episodes of cholangitis, decompensated cirrhosis, severe symptoms from widespread or pronounced biliary strictures and suspected early-stage biliary neoplasia (6).

In a word, this case suggests that early and active ERCP should not be delayed for acute severe biliary pancreatitis with uncontrolled cholangitis in fear of operative complications. In addition, PET/CT may offer reference to some extent for locating infection lesions for biliary drainage in SSC patients with uncontrolled infection, since drainage (e.g., PTCD or ERCP) in this condition is extremely cautious concerning about the difficulty and complication risks. More relevant studies are required for better understanding of SSC about potential mechanisms and possible treatment options.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this article were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying image resources.

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