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Case Report

Biliary Cast Syndrome and Secondary Sclerosing Cholangitis in Critically Ill Patient after Long-Term Treatment in the Intensive Care Unit

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Keywords
Biliary cast syndrome · Secondary sclerosing cholangitis · Cholestasis · ICU

Abstract
Introduction: Secondary sclerosing cholangitis in critically ill patients (SSC-CIP) is a rare but underdiagnosed entity that occurs after life-threatening events and treatment in the intensive care unit (ICU). The etiology of SSC-CIP is not fully understood but may be caused by ischemic bile duct injury. SSC-CIP is a cholestatic liver disease that rapidly progresses to liver cirrhosis, with a high mortality rate in the first year of 50%. Endoscopic retrograde cholangiopancreatography (ERCP), which is the gold standard for diagnosing SSC-CIP, shows primary SC-like changes, usually in the intrahepatic bile ducts. Biliary cast formation is pathognomonic for SSC-CIP. No proven effective conservative treatment is available for SSC-CIP, and liver transplantation is the only curative therapy when liver cirrhosis or recurrent cholangitis occurs. ***Case Presentation:*** We report the case of a 47-year-old male patient who developed cholestasis after a long treatment in the ICU for severe pneumonia. ERCP showed characteristic findings with rarefication and multiple segmental stenosis in the intrahepatic bile ducts. We removed multiple biliary casts from the bile ducts. ***Conclusion:*** SSC-CIP should be considered for ICU patients with unclear cholestasis, especially when the cholestasis persists after recovery from the underlying disease. Early diagnosis is important to achieve better outcomes; without liver transplantation, the prognosis is generally poor.

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Introduction

Secondary sclerosing cholangitis in critically ill patients (SSC-CIP) is a rare condition that develops after prolonged intensive care unit (ICU) treatment for life-threatening events, such as burns, polytrauma, major surgeries, and cardiopulmonary events [1, 2]. SSC-CIP is characterized by a cholestatic liver with rapid progression to liver cirrhosis, usually within months [1, 2]. The etiology is not fully understood and may be multifactorial. SSC-CIP is underdiagnosed by gastroenterologists and intensivists, probably due to the rarity of the disease and the multiple causes of cholestasis in ICU patients. Liver transplantation is the only valid therapy when cirrhosis or recurrent cholangitis develops. Thus, early diagnosis is necessary for organ allocation and to achieve better outcomes. The CARE Checklist has been completed by the authors for this case report, attached as online complementary material.

Case Presentation

A 47-year-old male patient experiencing homelessness was admitted to our hospital with respiratory distress and septic shock. The patient was an intravenous drug user and a heavy smoker (30 pack-years). Except for chronic hepatitis C, there was no history of liver or gastrointestinal disease. No relevant alcohol consumption was noted. Vital signs on admission showed hypotension (mean arterial pressure <65 mm Hg), tachycardia (heart rate = 130/m), and oxygen saturation of 80%. Laboratory tests on admission revealed leukocytosis (18,000/μL), elevated CRP (250 mg/dL; reference <5) and procalcitonin (2.2 ng/mL; reference <0.5), and very high liver enzymes (ALT 50 times the normal value, AST 100 times the normal value). The bilirubin, gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), and albumin levels were normal. The HCV-antibody test was positive, with a viral load of over 7 million IE/mL. The HIV test was negative. Computed tomography revealed bilateral pneumonia and abdominal ultrasonography revealed normal findings. Mechanical ventilation was initiated to treat the respiratory failure, and high-dose catecholamine was necessary for hemodynamic instability. The disease course was complicated by kidney infarction and paralytic ileus of the colon, which resolved after endoscopic decompression. After 1 week, the liver enzymes returned to normal range. After 10 days in the ICU, the patient was transferred to a tertiary hospital for extracorporeal membrane oxygenation therapy due to further respiratory deterioration. After 30 days of extracorporeal membrane oxygenation therapy, the patient was transferred back to our hospital. On the second admission, the liver tests were normal, except for slightly increased GGT. During the stay in the normal ward, we noted a gradual progression of the cholestatic parameters (GGT increased 30 times, ALP increased 10 times, and bilirubin was normal). Abdominal ultrasonography showed extrahepatic cholestasis with a common bile duct diameter of 12 mm and hyperechoic longitudinal material within the bile duct (Fig. 1). We removed multiple biliary casts from the bile ducts via ERCP (Fig. 2). The cholangiography showed rarefication with multiple segmental stenoses of the intrahepatic bile ducts (Fig. 3, 4). Therefore, the diagnosis of SSC-CIP was made. After the ERCP, the cholestasis parameters improved but did not return to normal ranges (GGT increased 10 times and ALP increased 5 times). During the second ERCP, no biliary casts were observed. To date, no signs of liver cirrhosis and no signs of recurrent cholangitis have been detected in our patient. We plan to follow up in 3 months.

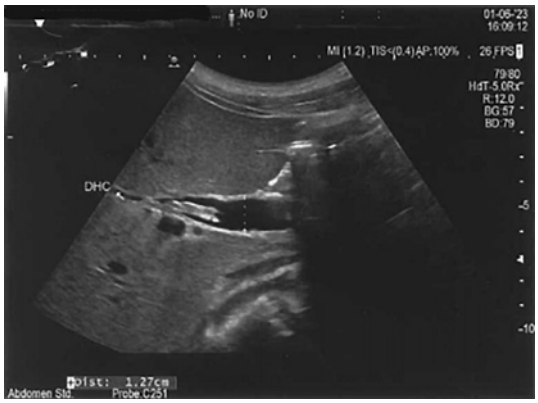

Fig. 1. Abdominal ultrasonography showed dilated common bile duct with cast formation.

Discussion

SSC-CIP is a rare condition following life-threatening events and ICU treatment. SSC-CIP was first well described by Schmitt in 1997 and Scheppach in 2001 [3, 4]. The estimated incidence of SSC-CIP in ICU patients is 0.05%. However, recent data showed a higher incidence (2.3%) in COVID-19 ICU patients [1, 5]. Reports about SSC-CIP have increased since the COVID-19 pandemic. Middle-aged men are predominantly affected [1, 2]. In patients with SSC-CIP, the average length of ICU treatment is 30–40 days, but the development of SSC-CIP after short-term ICU stays has also been reported [2].

SSC-CIP is characterized by a cholestatic liver pattern. GGT is the first parameter to increase; GGT is usually markedly elevated up to 30–50 times the normal value. ALP elevation is usually less markedly up to 15–20 times the normal value. Hyperbilirubinemia occurs later in the course of the disease or when liver cirrhosis develops. Liver enzymes (ALT/AST) are usually slightly elevated. Patients may report symptoms, such as pruritus or jaundice, but usually in the advanced stages [1, 2].

The etiology of SSC-CIP is not fully understood and may be multifactorial. The current data support an ischemic origin of the disease [5, 6]. The bile ducts receive blood supply from the hepatic artery. In contrast, both the portal vein and the hepatic artery provide blood supply to the liver cells. Thus, the bile ducts are more sensitive to hypoxemia and hemodynamic instability than the liver cells [6]. Ischemic injury of the bile epithelium leads to necrosis and destruction of the bile ducts. Data from our case support the ischemic hypothesis; our patient was hemodynamically unstable at admission, had a hypoxic liver injury demonstrated by highly elevated liver enzymes, and had a kidney infarction during the course of the disease. Another hypothesis is the "toxic bile concept," in which inflammatory mediators, such as TNF-alpha and other cytokines, lead to dysregulation of the hepatobiliary transporter system and alter the composition of bile acids. Altered bile acid composition can lead to the destruction of the bile ducts [5, 6]. Other suggested etiologies include medication, especially ketamine, bacterial translocation from the gut lumen to the hepatobiliary circulation, and genetic predisposition [3, 5, 6].

Abdominal ultrasonography helps exclude other diseases and suggests the diagnosis of SSC-CIP in only one-third of patients [2]. Cholangiography (ERCP or MRCP) is obligatory for diagnosing SSC-CIP. Typically, the extrahepatic bile ducts are spared or minimally changed, and pathological signs are usually observed in the intrahepatic bile ducts, including cast formation, irregularity, segmental stenosis, rarefication, and, in the advanced stages, destruction of the bile ducts [1]. Biliary cast formation is considered pathognomonic for SSC-CIP because this finding has not been reported in the other forms of sclerosing cholangitis, such as

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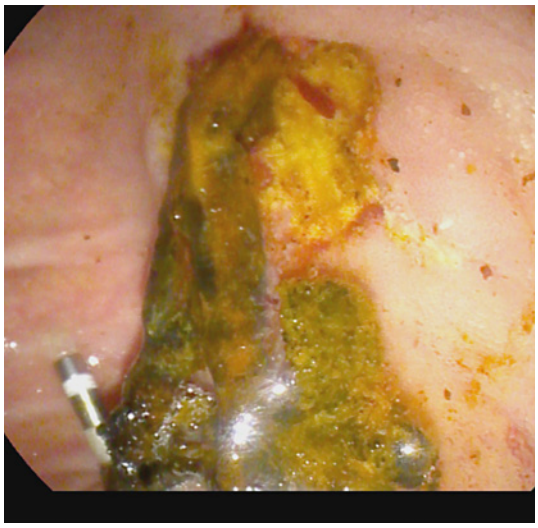

Fig. 2. ERCP with biliary cast removal from the bile duct.

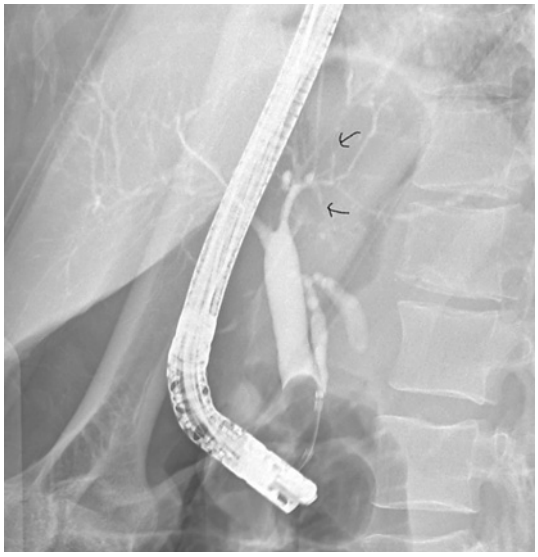

Fig. 3. Signs of SCC. Cholangiography showed rarefication and destruction (arrows) of the intrahepatic bile ducts.

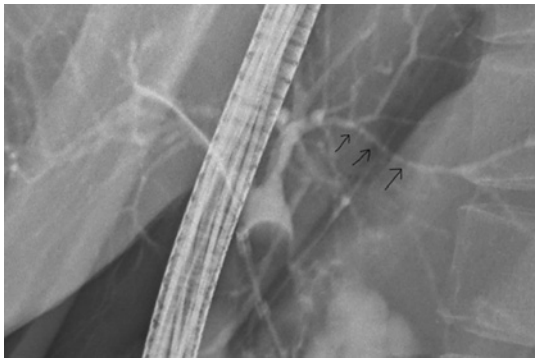

Fig. 4. Signs of SCC. Cholangiography showed multiple segmental stenosis in the intrahepatic bile ducts (arrows).

PSC or IgG4-related cholangitis [1]. The mechanism of cast formation in SSC-CIP is unclear but is presumed to be due to necrotic cholangiocytes and impaired bile flow [2]. Cast formation is also observed in some patients after liver transplantation and may also be due to ischemia [1, 2]. Liver biopsy has a limited value in establishing diagnosis because the histologic findings are nonspecific, especially in the early stage of the disease; however, liver biopsies help exclude other diseases [2, 7].

The differential diagnosis includes other causes of cholestasis in the ICU, such as sepsis, total parenteral nutrition, choledocholithiasis, drug injury, and hypoxic liver injury. However, in patients with SSC-CIP the cholestasis persists after recovery from the underlying disease. Other causes of sclerosing cholangitis include primary sclerosing cholangitis PSC, IgG4-related cholangitis, recurrent pyogenic cholangitis, HIV cholangiopathy, diffuse liver metastasis, postoperative bile duct injury, intra-arterial chemotherapy, portal hypertensive biliopathy, eosinophilic cholangitis, mast cell cholangiopathy, and some medications such as ketamine. Based on the patient history, imaging, and laboratory tests, these differential diagnoses can usually be excluded. In our patient, the level of IgG4 was normal and the HIV test was negative.

Complications of SSC-CIP include acute cholecystitis, recurrent cholangiosepsis due to recurrent cast formation and biliary stenoses, liver abscesses, and biliary cirrhosis [1]. Generally, SSC-CIP has a rapid progression into biliary cirrhosis, usually within months [1, 2]. Without liver transplantation, the prognosis is poor with a mortality rate of 50% within the first year [1, 2, 7]. The main cause of death is sepsis and liver failure [2, 7]. Cholangiocarcinoma has not been reported in patients with SSC-CIP [2, 7].

Ursodeoxycholic acid (UDCA) is commonly used in cholestatic liver disease, but the effects of UDCA on the course of the SSC-CIP are unknown. However, a survival benefit of UDCA was shown in one retrospective study [8]. Endoscopic treatment of biliary stenoses is difficult because they are usually multifocal and intrahepatic. Patients with sepsis should undergo ERCP with sphincterotomy and removal of biliary casts if they are found. In addition, balloon dilatation or stent implantation can be performed depending on the local findings [2]. A bile sample should be collected during ERCP because 98% of these patients have a positive bile culture [7]. Because of recurrent biliary cast formation and recurrent cholangitis, whether biliary intervention should be performed periodically or only with signs of cholangiosepsis is unclear. A multicenter prospective randomized study in Germany is in progress to address this issue [9].

The only curative therapy for SSC-CIP with recurrent cholangitis or biliary cirrhosis is liver transplantation. Several studies, including a meta-analysis, show very good long-term outcomes after transplantation with a survival rate of 83% at 3 years [1, 10]. Our patient probably has a mild form of SSC-CIP, and to date, he has no signs of liver cirrhosis or recurrent cholangitis. Therefore, the listing for liver transplantation is currently not needed. We started therapy with UDCA and planned a follow-up in 3 months. The patient was advised that ERCP would be necessary if there are signs of Cholangitis. Our patient also has untreated chronic hepatitis C, which has not previously been reported as a cause of SSC-CIP in the literature. However, chronic hepatitis C can lead to further damage to the liver, and thus, antiviral therapy is urgently recommended. The patient was referred also to the opioid replacement therapy and social support program.

The main learning point of this paper is to increase the awareness of the SSC-CIP, as cholestasis is seen frequently in ICU patients. SSC-CIP should be kept in mind in every ICU patient with a cholestatic liver pattern; otherwise, this relevant diagnosis may be missed.

Statement of Ethics

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. Ethical approval for this study was not required in concordance with the local/national guidelines.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

Funding Sources

No funding was received for this study.

Author Contributions

Alkurdi was involved in the clinical and endoscopic management of the patient, performed literature search, and wrote the article. Tschöpe, Herrmann, and Bekmukhametov were involved in the clinical management of the patient and reviewed the article.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files (for all online suppl. material, see https://doi.org/10.1159/000537957). Further inquiries can be directed to the corresponding author.

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