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Radiological patterns of secondary sclerosing cholangitis in patients after lung transplantation

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Abstract

Purpose: The purpose of this study was to investigate the radiological patterns of secondary sclerosing cholangitis (SSC) following lung transplantation.
Methods: Fifty-five patients underwent abdominopelvic CT before and after lung transplantation for end stage pulmonary disease. Nine patients underwent MR cholangiopancreatography (MRCP). The radiological patterns of biliary abnormalities (location, bile duct dilatation with stricture, beaded appearance, and biliary casts/sludge), laboratory data (serum total bilirubin and alkaline phosphatase), and patient survival rates were evaluated. SSC was diagnosed when there were newly developed biliary abnormalities with cholestasis after lung transplantation. Potential perioperative risk factors pertaining to SSC were analyzed. Patient survival rates with or without SSC were compared.
Results: Six of the 55 patients showed imaging and laboratory findings of SSC after lung transplantation. Multifocal dilatation and stricture involved the intrahepatic (6 of 6, 100%), hilar (4 of 6, 66.7%), and extrahepatic bile duct (1 of 6, 16.7%). On CT, the lesions presented as multifocal small cyst-like lesions along the bile duct course. On MRCP, the lesions showed beaded appearance with mild duct dilatation. Preoperative mechanical ventilation and bilateral lung transplantation were associated with SSC ($p < 0.05$). The median survival of patients with SSC was 4.6 months.
Conclusion: Lung transplantation can induce SSC similar to SSC in critically ill patients, and result in worse clinical outcomes than in patients without SSC. Multifocal small cyst-like lesions along the intrahepatic bile duct on CT and beaded appearance on MRCP are suggestive findings of SSC in patients with cholestasis after lung transplantation.

Key words: Secondary sclerosing cholangitis—Lung transplantation—CT—MRCP

Secondary sclerosing cholangitis (SSC) is a number of variably progressive cholestatic disease of the bile duct with identified causes, unlike primary sclerosing cholangitis (PSC) of idiopathic cause [1–3]. A new sub-entity of secondary sclerosing cholangitis has been defined in critically ill patients (SSC-CIP) in recent years [4–9]. This type of SSC occurs in association with intensive-care treatment of patients with major surgery, trauma, burns, and other life-threatening events [4–9]. The exact pathological mechanisms of SSC-CIP have not been elucidated conclusively, but are most likely caused by severe arterial hypotension or shock [4–9]. SSC-CIP is a progressive cholestatic liver disease characterized by necrosis of the bile duct epithelium, which leads to the rapid destruction of the bile ducts [4–9]. SSC-CIP has an irreversible course and less favorable prognosis than SSC of other causes such as drug, infection, or autoimmune diseases [4–9].

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Lung transplantation is the best treatment for patients with end stage pulmonary disease, and the number of lung transplantations has steadily increased [10–13]. As lung transplantation has become more widespread, several complications after lung transplantation have been reported [10–13]. Recently, we have encountered cases of SSC after lung transplants in our center. To our knowledge, however, the radiological findings of SSC in patients with lung transplants have never been reported. The aim of our study was to report the radiological patterns of SSC in patients after lung transplantation.

Materials and methods

This case series was approved by our institutional review board and the requirement for informed consent from patients was waived.

Patients

A total of 101 consecutive patients underwent lung transplantation for end-stage pulmonary disease between November 2012 and December 2016 at a single institution. Fifty-five patients underwent abdominopelvic CT before and after lung transplantation ($n = 55$). Nine patients underwent MR cholangiopancreatography (MRCP). Detailed baseline demographic and clinical characteristics of the patients are shown in Table 1.

Table 1. Baseline characteristics of patients with abdominopelvic CT after lung transplantation

Patient characteristics	Total patients ($n = 55$)
Age, year	52.6 ± 13.4
Male gender	30 (54.5)
Lung transplantation type, bilateral	11 (20)
Ever smoker	24 (43.6)
Primary lung disease	55 (100)
Idiopathic pulmonary fibrosis	30 (54.5)
Graft versus host disease after PBSCT	7 (12.7)
Interstitial lung disease associated with CTD	6 (10.9)
Lymphangioleiomyomatosis	3 (5.5)
Idiopathic pulmonary artery hypertension	2 (3.6)
Others	7 (12.7)
Previous liver disease	11 (20.0)
Hepatitis B virus carrier	6 (54.5)
Alcoholic liver disease	3 (27.3)
Cardiac cirrhosis	1 (9.1)
Hepatitis A virus infection	1(9.1)
Causes resulting in abdominopelvic CT	55 (100)
Abdominal pain or distension	19 (34.5)
Abnormal liver enzyme	9 (16.4)
Gastrointestinal tract bleeding	6 (10.9)
Sepsis	5 (9.1)
Underlying liver disease evaluation	5 (9.1)
Free air at simple abdominal X-ray	3 (5.5)
Others	8 (14.5)

Data are number (%) of patients or mean ± SD
PBSCT peripheral blood stem cell transplantation, *CTD* connective tissue disease

Biliary imaging analysis

We identified SSC after lung transplantation when all of the following conditions were met: (1) No bile duct dilatation or abnormality on CT imaging before lung transplantation; (2) newly developed intra- or extrahepatic bile duct dilatation and stricture on CT or MRCP after lung transplantation; and (3) elevated serum total bilirubin (> 1 mg/dL) and serum alkaline phosphatase (> 150 U/L) levels reflecting cholestasis.

Two board-certified abdominal radiologists with 13 and 17 years of experience in abdominal imaging retrospectively reviewed each pair of abdominopelvic CT images obtained before and after lung transplantation in consensus and analyzed the presence of biliary abnormality. If biliary abnormality was present, the following imaging features were recorded: extent and location (intrahepatic, hepatic hilum, extrahepatic), degree (mild, moderate, or severe) of dilatation and stricture, presence of beaded appearance, presence of bile duct wall thickening, and presence and location of biliary stones or casts. The presence or absence of acute cholecystitis was also evaluated. Both reviewers were aware that all patients had undergone lung transplantation, but blinded to the other clinical information, laboratory findings, and patient survival.

Clinical findings and patient survival

Clinical data before, during, and after transplantation were collected from electronic medical records by the third radiologist. The use of mechanical ventilator or extracorporeal membrane oxygenation (ECMO) was investigated before transplantation. The total ECMO time and hypovolemic event during transplantation were also investigated. Cytomegalovirus (CMV) infection, rejection, sepsis, hypovolemia due to bleeding, and other clinically threatened diseases occurring after transplantation were investigated. Serum total bilirubin, alkaline phosphatase levels, time to SSC, and the mean follow-up period were recorded. Patient survival rates after lung transplantation were calculated based on the date of lung transplantation until death or the date of last follow-up evaluation. Censoring was done at the last follow-up date for patients who were lost to follow-up.

CT and MR imaging protocol

All abdominopelvic CT images were obtained with a 64-channel CT scanner (Sensation 64, Siemens Medical Solutions, Forchheim, Germany; Brilliance 64, Philips Healthcare, Cleveland, OH, USA). After performing non-contrast CT, contrast-enhanced images were obtained 55 s after reaching 100 HU attenuation in the abdominal aorta with bolus tracking after intravenous administration of non-ionic contrast medium (Ultravist;

iopromide, Beyer Healthcare, Berlin, Germany and Omnipaque; iohexol, GE Healthcare, Cork, Ireland). The scanning parameters were as follows: beam collimation, 0.625 mm; slice thickness, 3 mm; reconstruction interval, 3 mm; pitch, 0.6; rotation time, 0.5 s; effective tube current–time charge, 170–240 mAs; 100–120 kVp.

Nine of 55 patients underwent MRCP with a 3.0-T scanner (Magnetom Trio Tim; Siemens Medical Solutions, Erlangen, Germany), using a 16-channel torso-array coil. Both single-section and navigator-triggered MRCP imaging were performed. Detailed MR imaging parameters are provided in Online Resource 1.

Statistical analysis

Clinical characteristics of the patients were compared between the SSC and non-SSC groups. The independent two-sample *t* test or Mann–Whitney *U* test was used for continuous variables, and the Chi-square test or Fisher's exact test was used for categorical variables. Patient survival was compared between the two groups by using Kaplan–Meier survival analysis and log-rank tests. All statistical analyses were performed using R software (version 3.3.1.; R Foundation for Statistical Computing, Vienna, Austria). All reported *p* values were two-sided with a significance level of < 0.05.

Results

Six of the 55 patients showed imaging and laboratory findings of SSC after lung transplantation (Figs. 1 and 2). Multifocal dilatation and stricture involve the intrahepatic duct from second order biliary radical to peripheral duct (6 of 6, 100%), hilar duct (4 of 6, 66.7%), and extrahepatic bile duct (1 of 6, 16.7%). On CT, the lesions presented as multifocal small cyst-like lesions along the course of the bile duct. On MRCP, the lesions showed beaded appearance with mild-degree duct dilatation. No patient exhibited bile duct wall thickening, biliary cast, or intrahepatic duct stones. Four patients had gallbladder stones without acute cholecystitis. The serum mean total bilirubin and alkaline phosphatase levels in 6 patients with SSC was 9.9 mg/dL (median, 4.3; range, 1.9–26.4 mg/dL) and 812 U/L (median, 732.5; range, 509–1274 U/L), respectively. The mean time to SSC after lung transplantation was 71 days (median, 70 days; range, 53–90 days).

The clinical factors associated with SSC were application of mechanical ventilation before lung transplantation and bilateral type lung transplantation (Table 2).

The mean follow-up period in 55 patients was 22.6 months (median, 16.9 months; range, 1.1–61.8 months). Overall survival rates 90 days, 180 days, and at last follow-up after lung transplantation in 49 patients without SSC were 90.8, 64.9, and 46.3%, respectively, whereas survival rates in 6 patients with SSC were 100, 100, and 0%, respectively ($p = 0.0008$) (Table 3 and Fig. 3). The median survival of patients with SSC was 4.6 months.

Discussion

Our cases of SSC in patients with lung transplantation showed mild intrahepatic bile duct dilatation with multifocal short segmental strictures. On CT, the lesions presented as multifocal small cyst-like lesions along the intrahepatic bile duct course. On MRCP, the lesions showed beaded appearance. All patients involved the peripheral intrahepatic duct. Only one patient had both intra- and extrahepatic duct abnormalities, and no patient had extrahepatic duct abnormalities only.

Unlike our cases, in most patients with liver transplantation SSC primarily involves the extrahepatic bile duct or hepatic hilar duct [14–17]. Blood supply to the bile duct comes solely from the peribiliary plexus of the terminal hepatic artery, which forms a rich microvascular network surrounding the bile ducts. Meanwhile, the majority of the blood supply from the hepatic artery is supplied by retroduodenal or retroportal arteries, which are responsible for the lower port of the bile duct [14, 18]. Therefore, the extrahepatic bile duct, especially the middle third of the common bile duct, is more vulnerable to biliary ischemia or necrosis rather than the intrahepatic bile duct. On the other hand, SSC-CIP is another cause of ischemic cholangiopathy, which is one of the subcategories causing SSC. Hemodynamic instability, mechanical ventilation, required vasopressor support, infection, or prone position in patients receiving intensive care treatment for a variety of life-threatening events have been known to be contributing factors to SSC-CIP [1, 14, 18]. These factors are thought to cause diffuse bile duct ischemia or necrosis more commonly in the intrahepatic bile duct rather than in the extrahepatic bile duct due to subacute to chronic state of sustained insufficient blood supply to the bile duct during a certain period [18]. Therefore, it may show a different pattern from the bile duct ischemia or necrosis due to acute bleeding events that often occur in patients after liver transplantation.

The radiological findings of our cases are similar to those of SSC in critically ill patients [4, 6, 7]. Abnormal bile duct conditions involved the intrahepatic bile duct in more than 87% of patients, whereas extrahepatic duct changes only were observed in less than 6% [4, 6]. Irregular intrahepatic bile ducts with multiple strictures and dilatations were observed on endoscopic retrograde cholangiopancreatography (ERCP), which is similar to PSC [4, 6, 7]. On ERCP, however, enhancement or thickening of the bile duct wall could not be evaluated. Our study using CT and MRCP showed no enhancement or thickening of the bile duct wall, which is different from PSC. Because there was no enhancement or thickening of the ductal wall in our study, the lesions looked

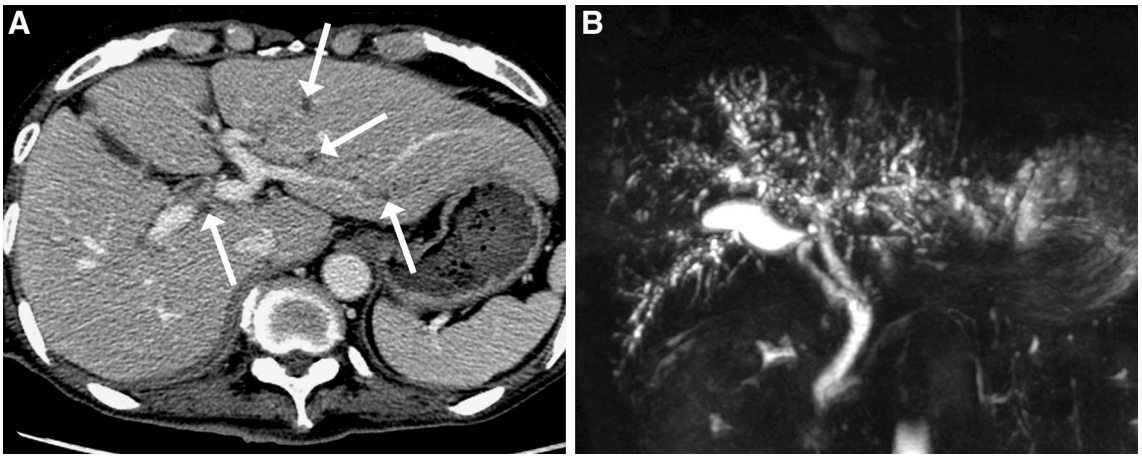

Fig. 1. A 66-year-old man who underwent bilateral lung transplantation for idiopathic pulmonary fibrosis. **A** CT image obtained 56 days after lung transplantation shows multifocal small cystic lesions (arrows) along the expected bilateral intrahepatic bile duct course, suggesting IHD dilatation. Bile duct wall thickening is not observed. **B** Two-dimensional MRCP performed 1 day after CT reveals mild multifocal intrahepatic duct dilatation with stricture from hepatic hilum to peripheral duct. Note that extrahepatic bile duct is normal in appearance.

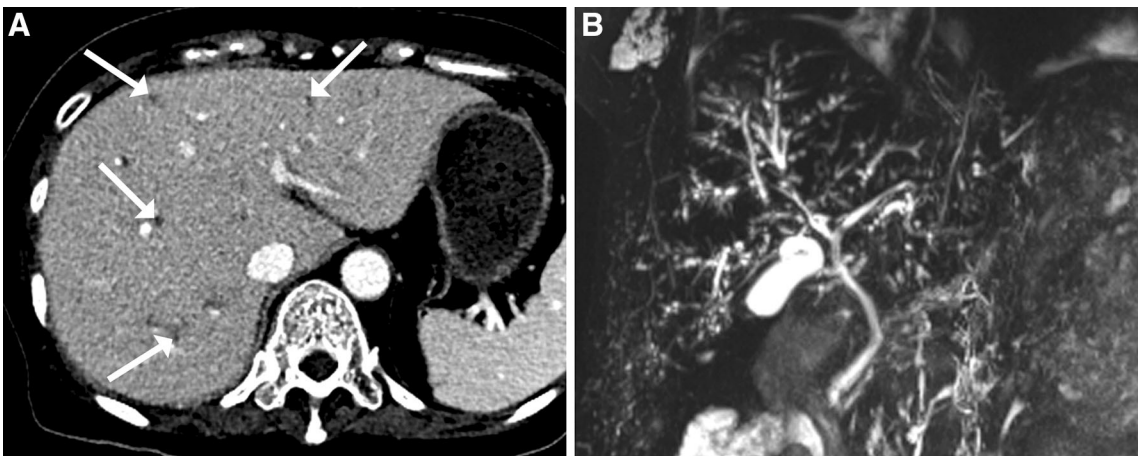

Fig. 2. A 54-year-old woman who underwent bilateral lung transplantation for bronchiolitis obliterans. **A** CT obtained 63 days after lung transplantation shows multifocal mild intrahepatic ductal dilatation (arrows). Bile duct wall thickening is not observed. **B** Two-dimensional MRCP performed 7 days after CT reveals multiple intrahepatic ductal dilatation with stricture from second order biliary radical to peripheral duct. Note that hepatic hilum and extrahepatic bile duct shows normal appearance and that involved intrahepatic bile ducts show multi-cystic appearance.

like small cysts along the bile duct on cross-sectional CT. On projectional MRCP images, the bile duct lesions showed beaded appearance similar to PSC.

Leonhardt et al. [4] reported three different cholangiographic features of SSC-CIP corresponding to the stages of pathogenesis: (I) early stage; evidence of biliary casts, (II) intermediate stage; progressive destruction of intrahepatic bile ducts, and (III) late stage; obliteration of the intrahepatic bile ducts/picture of the pruned tree. They suggested that as bile duct destruction progressed, from peripheral to the central duct, the pruned tree appearance would appear in the late stage. ERCP has been recommended for the diagnosis of SSC-CIP [4]. ERCP, however, is not only an invasive procedure but also plays a limited role in evaluating the intrahepatic bile duct distal to the obstruction. In our study, MRCP without contrast enhancement resulted in typical cholangiographic findings similar to those on ERCP and visualized all of the intrahepatic bile duct. Therefore, MRCP could replace ERCP for the diagnosis of SSC-CIP.

Critically ill patients encompass a wide range of patients with life-threatening conditions such as major cardiothoracic surgery, trauma, burns, or sepsis [5, 8, 9]. Because lung transplantation is major surgery requiring the intensive care unit treatment during the perioperative period, it is plausible that lung transplantation is associated with SSC-CIP. The number of lung transplants

Table 2. Comparison of perioperative and postoperative risk factors between patients with and without secondary sclerosing cholangitis

Factors	Patients with secondary sclerosing cholangitis (n = 6)	Patients without secondary sclerosing cholangitis (n = 49)	p
Recipient			
Age	58.8 ± 6.2 (61; 49–66)	51.8 ± 13.9 (55; 17–71)	0.3045[a]
Sex, male	4 (66.7%)	26 (53.1%)	0.6779[b]
Ever Smoker	2 (33.3%)	22 (44.9%)	0.6862[b]
Previous liver disease	2 (33.3%)	7 (14.3%)	0.2513[b]
Perioperative factors			
Lung transplantation, bilateral	6 (100%)	5 (10.2%)	< 0.0001[b]
Pre-mechanical ventilation	5 (83.3%)	8 (16.3%)	0.0019[b]
Pre-ECMO	2 (33.3%)	8 (16.3%)	0.2976[b]
Total ECMO time	10395.7 ± 16311.5 (614; 308–38858)	3357.4 ± 5823.2 (420; 160–23,860)	0.2457[a]
Postoperative factors			
Cytomegalovirus infection	5 (83.3%)	41 (83.7%)	> 0.9999[b]
Hypovolemic event	0 (0%)	7 (14.3%)	> 0.9999[b]
Sepsis	4 (66.7%)	19 (38.8%)	0.2234[b]
Rejection	0 (0%)	7 (14.3%)	> 0.9999[b]
Other factors associated with elevated total bilirubin			
HLH	1 (100%)	1 (100%)	–
Bleeding	0 (100%)	2 (100%)	–
Thrombotic microangiopathy	0 (100%)	4 (100%)	–

ECMO extracorporeal membranous oxygenation, *HLH* hemophagocytic lymphohistiocytosis
[a]Continuous values are mean ± SD with median and minimum to maximum in parentheses
[b]Categorical values are numbers with percentages in parentheses

Table 3. Survival rates (%) in patients with lung transplantation

Time after lung transplantation	Patients with secondary sclerosing cholangitis (n = 6)	Patients without secondary sclerosing cholangitis (n = 49)	p
30 Days survival	100	100	–
90 Days survival	100	89.7	–
Last survival	0	52.2	0.0008

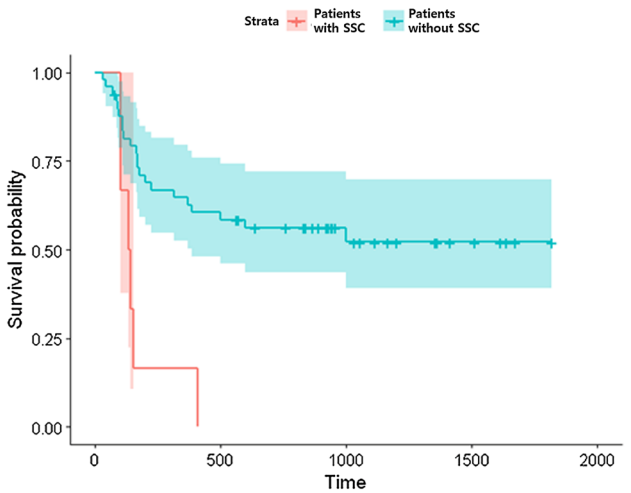

Fig. 3. Kaplan-Meier survival analysis of patients with secondary sclerosing cholangitis (SSC) and without SSC after lung transplantation. Patients with SSC showed that they had a significantly lower survival rate than those without SSC (p = 0.0008).

has steadily increased worldwide, although patient survival rates after lung transplantation are consistently lower than those of other solid organ transplantations. The mean overall survival of patients with SSC after lung transplantation in our study was only 4.6 months. We found that preoperative mechanical ventilation was associated with SSC after lung transplantation. This result was consistent with previous reports [1, 5]. However, other known risk factors such as transplant rejection or CMV infection were not associated with SSC in this study. CMV is one of the most frequently infected viruses after lung transplantation and its related vasculitis were known as inducing ischemic cholangiopathy [11, 14]. With regard to sepsis as a possible cause of ischemic cholangiopathy, there was no association between patients with and without SSC. Further studies to identify risk factors of SSC after lung transplantation are needed.

Our study has inevitable limitations related to its retrospective study design and small number of cases. Thus, the findings of SSC after lung transplantation detected in our study cannot be generalized. Lung transplantation is not a widely performed operation, but the

identification and treatment of SSC after lung transplantation is critical. Therefore, clinicians and radiologists should be aware of the clinical significance and be familiar with the radiological findings of SSC after lung transplantation.

In conclusion, lung transplantation can induce SSC, similar to SSC in critically ill patients, and result in worse clinical outcomes compared to those of patients without SSC. Multifocal small cyst-like lesions along the intrahepatic bile duct on CT and beaded appearance on MRCP are suggestive findings of SSC in patients with cholestasis after lung transplantation.

Compliance with ethical standards

Funding No funding was received for this retrospective study.

Conflict of interest The authors declare that they have no conflict of interest.

Disclosures of potential conflicts of interest There is no any direct or potential financial disclosure for each author.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent Need of informed consent was waived since this study was performed retrospectively.

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