Original Article

Rare causes of hyperbilirubinemia after lung transplantation: our experience at a single center

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Background: Lung transplantation is the last treatment option for end-stage lung disease, and the number of lung transplantations has been steadily increasing. Hyperbilirubinemia is a rare complication after lung transplantation. The aim of this study was to review rare causes of hyperbilirubinemia after lung transplantation at our center.

Methods: In this single-center study, we retrospectively reviewed the records of 116 consecutive lung transplantation patients who underwent lung transplantation at Severance Hospital and Gangnam Severance Hospital of Yonsei University College of Medicine in South Korea between December 22, 2010 and January 1, 2016. Hyperbilirubinemia was defined as a total bilirubin level exceeding 5 mg/dL for at least 3 days after lung transplantation.

Results: Hyperbilirubinemia occurred in 33 patients (28.4%) who received lung transplants at our institution. Twenty-four cases involved common causes such as drug toxicity, biliary tract stone, sepsis, and bleeding. However, rare causes of hyperbilirubinemia including hemophagocytic lymphohistiocytosis (HLH), thrombotic microangiopathy (TMA), and ischemic cholangiopathy were observed in 9 (7.8%) patients during the study period. All patients with hyperbilirubinemia due to a rare cause died despite aggressive treatment.

Conclusion: Causes of hyperbilirubinemia after lung transplantation are varied, and the prognosis of patients with hyperbilirubinemia arising from rare causes was poor. Therefore, early evaluation and management of hyperbilirubinemia after lung transplantation is important to improve patient outcomes.

Keywords: Lung transplantation; hyperbilirubinemia; hemophagocytic lymphohistiocytosis (HLH); thrombotic microangiopathy (TMA); ischemic cholangiopathy

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Introduction

Bilirubin is the catabolic end-product of heme metabolism which originates from the degradation of erythrocyte hemoglobin in the reticuloendothelial system, inefficient erythropoiesis in bone marrow, and degradation of other heme proteins (1). The level of serum total bilirubin is widely used to identify hepatobiliary function and hemolytic diseases (2). The etiology of hyperbilirubinemia

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is multifactorial and includes advanced liver disease, sepsis, and bleeding (3,4). Thus, clearly identifying the cause of persistent hyperbilirubinemia is essential to guide subsequent treatment (3,4).

Lung transplantation has become an established treatment option for patients with end-stage lung disease, and the number of lung transplantations has steadily increased (5). As lung transplantation has become more widespread, several complications after lung transplantation have been reported (6,7). Hyperbilirubinemia after organ transplantation has been reported (8-10), and we have encountered rare causes of hyperbilirubinemia after lung transplantation at our center. Previous research reported that hyperbilirubinemia is common among patients with pulmonary hypertension and that these patients have greater mortality during heart–lung transplantation (11). However, most cases of hyperbilirubinemia were associated with transplantation of organs other than the lungs.

In this study, we investigated the cause, frequency, prognosis and clinical characteristics of unexpected and rare causes of hyperbilirubinemia after lung transplantation.

Methods

Study design

This study was a retrospective case series of patients who were developed hyperbilirubinemia after lung transplantation. Between December 22, 2010 and January 01, 2016, 116 patients underwent lung transplantation at Severance Hospital and Gangnam Severance Hospital in South Korea.

All donor lungs were transplanted from patients after brain death and preserved using low-potassium dextran solution (Perfadex®; Duraent Biologicals, Hyderabad, India). During lung transplantation surgery, extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass was applied to all patients for cardiopulmonary support. All patients were received corticosteroids for immunosuppression at the time of transplantation surgery and maintained on triple immunosuppression therapy including prednisolone, tacrolimus, and mycophenolate mofetil (MMF) after transplantation.

Data collection and definition

The normal range of serum total bilirubin at our center is between 0.4 and 1.5 mg/dL. We defined hyperbilirubinemia as total bilirubin level exceeding 5 mg/dL for at least 3 days after lung transplantation. We defined common cause of hyperbilirubinemia that included drug toxicity, sepsis, biliary tract stone, bleeding and other clinically easily predicted causes. Patient data such as demographic, laboratory, mortality, medications, imaging, and other data were collected from the hospital's electronic medical records.

Statistical analysis

Data were expressed as median plus range or interquartile range. Statistical analyses were performed with SPSS version 23 statistical software. Differences between rare causes of hyperbilirubinemia group and common causes of hyperbilirubinemia group were compared using the Mann Whitney U test. $P<0.05$ were considered statistically significant.

Results

A total of 116 patients received lung transplantation, and 33 (28.4%) lung transplant recipients developed hyperbilirubinemia during the study period (*Table 1*). The leading cause of lung transplantation was idiopathic pulmonary fibrosis (48.3%), followed by bronchiolitis obliterans after stem cell transplantation (12.1%) and interstitial lung disease related to connective tissue disease (10.3%). Ten patients out of 116 patients had chronic liver disease. Among them, four patients had mild fatty liver disease, four patients had well controlled chronic hepatitis B, one patient had alcoholic liver disease, and one had liver failure. The patient with liver failure patient underwent simultaneous lung and liver transplantation.

Among the 33 patients with hyperbilirubinemia, 24 patients had common causes of hyperbilirubinemia such as drug toxicity, biliary tract stone, sepsis, bleeding, and liver failure after lung transplantation with liver transplantation. Nine patients had unexpected, rare causes of hyperbilirubinemia including hemophagocytic lymphohistiocytosis (HLH), thrombotic microangiopathy (TMA), and ischemic cholangiopathy.

The baseline characteristics of patients with hyperbilirubinemia after lung transplantation are described in *Table 2*. The most common cause of hyperbilirubinemia was sepsis (N=11, 33.3%). Patients who developed hyperbilirubinemia had a poor prognosis, and the recovery

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Table 1 Characteristics of all patients who underwent lung transplantation surgery

Variables	Total patients (N=116)
Age, year	53.5 [16–75]
Male gender	64 (55.2)
BMI, kg/m^2, median (IQR)	19.7 (17.6–23.2)
LTx type, bilateral	106 (91.4)
Ventilator before LTx	40 (34.5)
ECMO before LTx	23 (19.8)
Ever smoker	49 (42.2)
90 days survivor	92 (79.3)
180 days survivor	73 (62.9)
Patients with hyperbilirubinemia	33 (28.4)
Primary cause of lung transplantation	
COPD/emphysema	2 (1.7)
IPF	56 (48.3)
Idiopathic pulmonary arterial hypertension	2 (1.7)
Pulmonary fibrosis, other: NSIP, AIP	9 (7.8)
Bronchiectasis	8 (6.9)
Bronchiolitis obliterans syndrome after SCT	14 (12.1)
Interstitial lung disease related with connective tissue disease	12 (10.3)
LAM	9 (7.8)
Others*	4 (3.4)

Data are shown as number (%) or median (range). *, chronic hypersensitivity pneumonitis, destroyed lung, langerhans cell histiocytosis. BMI, body mass index; IQR, interquartile range; LTx, lung transplantation; ECMO, extracorporeal membrane oxygenation; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonia; AIP, acute interstitial pneumonia; SCT, stem cell transplantation; LAM, lymphangioleiomyomatosis.

rate of hyperbilirubinemia was low (N=5, 15.2%). Causes of normalized hyperbilirubinemia were bleeding, drugs, and biliary tract stones. Four of the five patients who recovered from hyperbilirubinemia were still alive at the 180-day follow-up, and the remaining 29 patients with hyperbilirubinemia expired within 180 days after lung transplantation. Sepsis was the leading cause of death (N=16), followed by liver failure due to ischemic cholangiopathy (N=4), TMA (N=3), HLH (N=2), bleeding (N=2) and sudden cardiac arrest (N=2). Median age, male sex, and median body mass index did not differ according to cause of hyperbilirubinemia. However, the median onset time of hyperbilirubinemia after lung transplantation in cases with rare causes was relatively late (88 *vs.* 6.5 days, P<0.001) compared to cases with common causes. Three patients among those with hyperbilirubinemia had liver disease and no distinct types were noted.

The demographic characteristics of the 9 patients with rare causes of hyperbilirubinemia are presented in *Table 3*. Two patients had HLH, and both were intubated and mechanically ventilated before transplantation. Patients underwent imaging using abdominal ultrasonography, abdominal computed tomography (CT), or magnetic resonance cholangiopancreatography (MRCP) after developing hyperbilirubinemia. However, imaging studies did not reveal abnormalities in the biliary tract or liver parenchyma. Patients had hyperbilirubinemia with ongoing pancytopenia of unknown origin. Various laboratory tests were performed (*Table S1*); however, the reason for pancytopenia was not determined. Finally, bone marrow aspiration and biopsy were conducted. HLH was diagnosed based on the clinical findings, laboratory findings, and bone marrow biopsy results.

Three patients were diagnosed with TMA. None were intubated or mechanically ventilated before transplantation. All underwent abdominal imaging with ultrasonography and CT upon detection of hyperbilirubinemia. However, imaging did not reveal abnormalities in the biliary tract or liver parenchyma. We conducted a peripheral blood smear due to thrombocytopenia and discovered schistocytes. Additionally, the haptoglobulin level was low, and the reticulocyte level was high, which suggested hemolytic anemia. One patient underwent a bone marrow biopsy, which showed nonspecific findings. To evaluate microangiopathic hemolytic anemia (MAHA), ADAMTS13 activity was evaluated in two patients and found to be normal or only mildly decreased (*Table S1*). We supposed that hyperbilirubinemia was caused by TMA, which might be related to the use of tacrolimus.

Four patients were diagnosed with ischemic cholangiopathy. Three were intubated and mechanically ventilated before transplantation. Patients underwent abdominal imaging with several modalities including ultrasonography, CT, and MRCP. Imaging studies revealed features of ischemic cholangiopathy and no obstruction of the biliary tract (*Figure 1*). Case 6 was diagnosed after undergoing endoscopic retrograde

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Table 2 Baseline characteristic of hyperbilirubinemia patients after lung transplantation

Variables	Total, N=33	Rare causes, N=9	Common causes, N=24	P
Age, year	60 [17–73]	62 [27–73]	58 [17–72]	0.437
Male gender	24 (72.7)	5 (55.6)	19 (79.2)	0.212
BMI, kg/m^2, median (IQR)	21.3 (19.2–23.5)	19.9 (17.3–22.7)	21.4 (19.4–24.7)	0.193
LTx type, bilateral	31 (93.9)	8 (88.9)	23 (95.8)	0.477
Interval between onset of hyperbilirubinemia and LTx, day	21 [0–143]	88 [48–143]	6.5 [0–137]	<0.001*
Peak bilirubin level	18 (5.9–49.6)	18 (12.7–31.2)	19.2 (12.4–27.8)	0.953
Normalization of bilirubin	5 (15.2)	0 (0)	5 (20.8)	0.290
Liver disease before LTx†	3 (9.1)	2 (22.2)	1 (4.2)	0.174
DM	6 (18.2)	2 (22.2)	4 (16.7)	1.000
Cardiovascular disease	7 (21.2)	3 (33.3)	4 (16.7)	0.358
Ventilator before LTx	17 (51.5)	5 (55.6)	12 (50.0)	1.000
ECMO before LTx	11 (33.3)	2 (22.2)	9 (37.5)	0.681
Ever smoker	17 (51.5)	4 (44.4)	13 (54.2)	0.708
90 days survivor	18 (54.5)	8 (88.9)	10 (41.7)	0.021*
180 days survivor	4 (12.1)	0 (0)	4 (16.7)	0.555
Primary cause of LTx				0.299
IPF	23 (69.7)	6 (66.7)	17 (70.8)	
Pulmonary fibrosis, other	4 (12.1)	2 (22.2)	2 (8.3)	
Bronchiolitis obliterans syndrome after SCT	2 (6.1)	0 (0)	2 (8.3)	
Idiopathic pulmonary arterial hypertension	1 (3.0)	1 (11.1)	0 (0)	
Interstitial lung disease related with connective tissue disease	3 (9.1)	0 (0)	3 (12.5)	
Cause of hyperbilirubinemia				–
Ischemic cholangiopathy	4 (12.1)	4 (44.4)	–	
HLH	2 (6.1)	2 (22.2)	–	
TMA	3 (9.1)	3 (33.3)	–	
IHD stone, GB stone	3 (9.1)	–	3 (12.5)	
Drug	3 (9.1)	–	3 (12.5)	
Bleeding	2 (6.1)	–	2 (8.3)	
Sepsis	11 (33.3)	–	11 (45.8)	
Others‡	5 (15.2)	–	5 (20.8)	

Data are shown as number (%) or median (range). †, Alcoholic liver cirrhosis, Chronic Hepatitis; ‡, liver transplantation, shock, unknown; *, significant at P<0.05. IQR, interquartile range; BMI, body mass index; LTx, lung transplantation; DM, diabetic mellitus; ECMO, extracorporeal membrane oxygenation; IPF, idiopathic pulmonary fibrosis; SCT, stem cell transplantation; HLH, hemophagocytic lymphohistiocytosis; TMA, thrombotic microangiopathy; IHD, intrahepatic duct; GB, gallbladder.

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Table 3 Baseline characteristics of patients who developed hyperbilirubinemia due to atypical causes after lung transplantation

Variables	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Cause of hyperbilirubinemia	HLH	HLH	TMA	TMA	TMA	Ischemic cholangiopathy	Ischemic cholangiopathy	Ischemic cholangiopathy	Ischemic cholangiopathy
Age, years	61	53	73	63	59	27	68	63	50
Sex	Male	Female	Male	Male	Female	Female	Male	Male	Female
BMI kg/m^2	19.2	22.5	27.4	20.9	19.9	23.0	12.5	17.5	17.1
Reason for transplant	IPF	COP	IPF	IPF	IPF	AIP	IPF	IPF	PPAH
Year of transplant	2013	2014	2013	2015	2015	2011	2013	2014	2015
Type of transplant	Bilateral	Bilateral	Single	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral
Induction	Corticosteroid	Corticosteroid	Corticosteroid	Corticosteroid	Corticosteroid	Corticosteroid	Corticosteroid	Corticosteroid	Corticosteroid
Maintenance immunosuppression	Tacrolimus, MMF, corticosteroid	Tacrolimus, MMF, corticosteroid	Tacrolimus, MMF, corticosteroid	Tacrolimus, MMF, corticosteroid	Tacrolimus, MMF, corticosteroid	Tacrolimus, MMF, corticosteroid	Tacrolimus, MMF, corticosteroid	Tacrolimus, MMF, corticosteroid	Tacrolimus, MMF, corticosteroid
Comorbidity	None	None	CAD, DM, HTN	CAD, DM, HTN	Cancer history	None	Old CVA,	DM	Chronic hepatitis B, HTN, CHF
Onset of bilirubin 5 mg/dL	POD 52	POD 68	POD 133	POD 101	POD 143	POD 88	POD 89	POD 60	POD 48
ECMO before transplant	No	Yes	No	No	No	Yes	No	No	No
Ventilator before transplant	Yes	Yes	No	No	No	Yes	Yes	Yes	No
Laboratory test during peak bilirubin level									
Total bilirubin, mg/dL	42.7	15.3	10.1	9.8	17.7	18	25.9	26.6	35.8
Direct bilirubin, mg/dL	34.4	13	–	4.3	13.5	14.1	19.2	23.1	28.2
Gamma-GT, IU/L	201	1393	–	808	290	378	244	440	534
ALK, IU/L	336	434	–	143	45	274	272	858	598
LDH, IU/L	189	612	481	629	1726	900	357	520	597

Table 3 *(continued)*

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Table 3 *(continued)*

Variables	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Abdominal imaging tests	Sonography, CT	Sonography, CT, MRI	CT	Sonography, CT	Sonography, CT	Sonography, CT, MRI, ERCP	Sonography, CT, MRI	Sonography, CT	Sonography, CT, MRI
Treatment	Etoposide plus corticosteroid	Corticosteroid	Plasmapheresis, change from tacrolimus to basiliximab	Plasmapheresis, change from tacrolimus to basiliximab	Plasmapheresis, change from tacrolimus to basiliximab	ERBD, supportive care	Supportive care	Supportive care	PTBD, supportive care
Survival days	POD 87	POD 133	POD 142	POD 114	POD 164	POD 152	POD 153	POD 103	POD 141
Outcome	Died	Died	Died	Died	Died	Died	Died	Died	Died

HLH, hemophagocytic lymphohistiocytosis; TMA, thrombotic microangiopathy; BMI, body mass index; IPF, idiopathic pulmonary fibrosis; COP, cryptogenic organizing pneumonia; AIP, acute interstitial pneumonia; PPAH, primary pulmonary arterial hypertension; MMF, mycophenolate mofetil; CAD, coronary artery disease; DM, diabetic mellitus; HTN, hypertension; CVA, cerebrovascular accident; CHF, congestive heart failure; POD, postoperative day; ECMO, extracorporeal membrane oxygenation; gamma-GT, gamma-glutamyl transferase; ALK, alkaline phosphatase; LDH, lactate dehydrogenase; CT, computed tomography; MRI, magnetic resonance imaging; ERCP, endoscopic retrograde cholangiopancreatography; ERBD, endoscopic retrograde biliary drainage; PTBD, percutaneous transhepatic biliary drainage.

cholangiopancreatography (ERCP), liver biopsy and imaging. The ERCP revealed small filling defects and dilatation of both intrahepatic ducts. Liver biopsy in case 6 revealed intrahepatic cholestasis and portal widening with acute inflammatory cell infiltration. The result of the liver biopsy in case 7 revealed the development of cholestatic hepatitis. Cases 8 and 9 were diagnosed without liver biopsy because these patients had very similar findings with regard to laboratory studies, imaging studies, and clinical characteristics as cases 6 and 7.

The time interval between transplantation and hyperbilirubinemia was approximately 2 months in patients with HLH and ischemic cholangiopathy, and approximately 4 months in patients with TMA (*Table 3*).

The two patients diagnosed with HLH were treated with etoposide plus steroid or steroid alone, and the three patients who developed TMA had their treatment changed to basiliximab from tacrolimus with plasmapheresis. The four patients with ischemic cholangiopathy received supportive treatment including endoscopic retrograde biliary drainage or percutaneous transhepatic biliary drainage. However, all nine patients with hyperbilirubinemia of rare causes died due to progression of HLH, TMA or ischemic cholangiopathy during long term intensive care unit treatment (*Table 3*).

Discussion

In the present study, we found that hyperbilirubinemia occurred at a rate of 28.4% (33/116) in patients who received lung transplants at our institution, and the rate of hyperbilirubinemia due to rare causes such as HLH, TMA, and ischemic cholangiopathy was 7.8% (9/116) during the study period.

We further found that most causes of severe hyperbilirubinemia were not hepatic but systemic problems and associated with poor prognosis. In our institution, the most common cause of 1-year mortality was infection (58.3%), followed by cardiac arrest (12.5%) and TMA (12.5%). Some patients died due to HLH, ischemic cholangiopathy, or bleeding. Except sudden cardiac arrest, most causes of mortality could induce hyperbilirubinemia (12).

HLH is a potentially life-threatening hyperinflammatory syndrome that is divided into primary and secondary (or acquired) HLH. Our cases were secondary HLH. Acquired HLH without a genetic cause develops due to infections, autoimmune diseases, malignancies or

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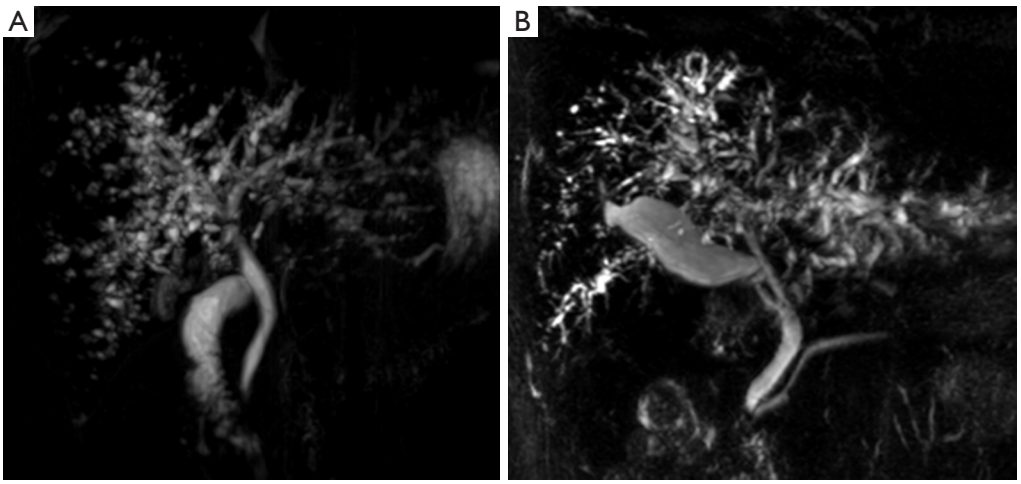

Figure 1 MRI imaging of ischemic cholangiopathy patients. (A) Showed innumerable irregular small cystic lesions along the entire IHD and dilated IHD with multifocal stricture including the hilar portion without demonstrable mass lesion; (B) showed multifocal irregular beaded appearance and wall thickening of the IHD. There were not definitely visualized stones in IHD or CBD. MRI, magnetic resonance imaging; IHD, intrahepatic duct; CBD, common bile duct.

other stimuli. A number of clinical symptoms can be observed in patients with HLH including persistent fever, multiple organ involvement, and laboratory abnormalities including cytopenia, increased serum ferritin level, abnormal liver function tests (aspartate transaminase, alanine aminotransaminase, gamma-glutamyl transferase, bilirubin, lactate dehydrogenase), and abnormal coagulation parameters. High-dose corticosteroid, etoposide, and cyclosporine have been suggested as treatments for primary HLH. However, a treatment regimen for acquired HLH does not yet exist, and the prognosis of acquired HLH is poorer than that of primary HLH (13). The poor prognosis of our cases with acquired HLH after lung transplantation is consistent with previous reports (14,15). In patients who undergo lung transplantation, the immune system is altered by the use of immunosuppressive drugs. Therefore, these patients are at high risk of opportunistic infection and sepsis. We speculate that infection and severe inflammation in our cases were associated with HLH after lung transplantation. Although the pathogenesis of acquired HLH remains unclear, several studies suggest that HLH is associated with inflammation (16-18). Furthermore, in many patients, HLH may be accompanied by hepatitis, because HLH induces excessive inflammation and tissue destruction (19). Therefore, HLH should be considered in the differential diagnosis of hyperbilirubinemia after lung transplantation when the origin of hyperbilirubinemia is unknown.

TMA induced by various causes is characterized by MAHA, thrombocytopenia, microvascular thrombosis, and organ injury (20). Several drugs associated with TMA have been reported (20,21). These drugs mediated TMA through immune or toxic dose-duration-related reactions (20). In an analysis of 387 articles, Al-Nouri *et al.* reported that 22 drugs had definite evidence of association with TMA, three of which (quinine, cyclosporine, and tacrolimus) accounted for approximately 58 percent of drug-induced TMA cases (21). We speculate that the TMA cases in our study were associated with tacrolimus, because all patients developed hyperbilirubinemia after at least 3 months of immunosuppressive therapy, and TMA temporarily improved after stopping the use of tacrolimus with plasma exchange. Furthermore, we could not find other causes of TMA. ADAMTS13 activity and complement level support this diagnosis. MAHA, which is caused by TMA, increases the indirect bilirubin level by destroying red blood cells. Therefore, TMA should be considered in the differential diagnosis of hyperbilirubinemia of unknown origin after lung transplantation, because urgent management in suspected TMA is important (22).

Ischemic cholangiopathy is induced by impaired blood supply, especially the peribiliary vascular plexus from hepatic arteries (23). Ischemic cholangiopathy can have various causes including liver transplantation, vascular injury during surgery, chemotherapy, biliary ischemia in hereditary hemorrhagic telangiectasia, or

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secondary sclerosing cholangitis in critically ill patients (23,24). Patients with ischemic cholangiopathy present with clinical features including jaundice, pruritus, and dark urine. Although there are several radiological features of primary sclerosing cholangitis, abdominal ultrasonography or CT can reveal normal findings. Therefore, the diagnosis of ischemic cholangiopathy generally requires magnetic resonance imaging (MRI) or cholangiography (23,25). Liver transplantation is the most common cause of ischemic cholangiopathy (23); however, ischemic cholangiopathy after lung transplantation has not been previously reported. We speculate that our cases were associated with prolonged hypoxic damage due to ventilator care before transplantation and septic shock after transplantation. In view of prolonged ischemia, several papers have reported on the relationship between critical illness and ischemic cholangiopathy (24,26,27). Abbasi *et al.* reported that longer duration of ECMO and ECMO-related complications were associated with the development of cholestasis in neonates (28). In our study, only one of our patients with ischemic cholangiopathy had experienced ECMO before lung transplantation. Seventeen patients with hyperbilirubinemia weaned the ECMO in the intensive care unit (ICU) after lung transplantation. One out of 17 patients was diagnosed with ischemic cholangiopathy. There was no association between delayed ECMO weaning or duration of ECMO use and cause of hyperbilirubinemia. Therefore, the relationship between ECMO and ischemic cholangiopathy was unclear in our study. The optimal treatment of ischemic cholangiopathy has not yet been established (23). Despite efforts including endoscopic retrograde biliary drainage and percutaneous transhepatic biliary drainage, all our patients died. Taken together, ischemic cholangiopathy should also be considered in the differential diagnosis of hyperbilirubinemia when patients have been exposed to shock or have findings of obstructive jaundice without a definite obstruction on abdominal ultrasonography or CT.

Although causes of hyperbilirubinemia can vary widely (3,4), only few cases of hyperbilirubinemia with rare causes after lung transplantation have been reported (14,15,29-31). Furthermore, we did not find any reports on the association of lung transplantation with ischemic cholangiopathy. Patients with rare causes of hyperbilirubinemia after lung transplantation had a poor prognosis; therefore, early evaluation and management of hyperbilirubinemia are essential to improving prognosis. Several imaging studies including abdominal ultrasonography, CT, and MRI; clinical manifestations; time interval between transplantation and hyperbilirubinemia detection; and various laboratory tests may be helpful for the differential diagnosis of causes of hyperbilirubinemia.

This study has several limitations. First, the sample size is relatively small. Second, this study is a retrospective analysis and a single-center experience. Third, we cannot rule out the effects of cardiopulmonary support because we used ECMO or cardiopulmonary bypass during all operations. Finally, patients who developed hyperbilirubinemia may have complex, multifactorial causes of hyperbilirubinemia and we were unable to account for all of these due to the retrospective nature of this study. Additional prospective and multicenter studies are needed to assess the incidence, causes, prognosis, and risk factors of hyperbilirubinemia after lung transplantation.

Conclusions

Causes of hyperbilirubinemia after lung transplantation are varied, and the prognosis of patients with rare causes of hyperbilirubinemia was poor. Therefore, early evaluation and management of hyperbilirubinemia may be necessary if it develops after lung transplantation.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study protocol was approved by the Institutional Review Board (IRB) of Severance Hospital (IRB number: 2013-0522-019). Informed consent was waived by the IRB because of the study's retrospective nature.

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Supplementary

Table S1 Specific studies of each patient due to hyperbilirubinemia

Number, cause of hyperbilirubinemia	Specific tests among patients
Case 1, HLH	BM study: histiocytosis with occasional hemophagocytes is noted; increased number of stromal macrophages (CD68)
	Haptoglobin: 42.99 mg/dL [30–200]
	Serum ferritin: 2,495.5–4,518.2 ng/mL (23.9–336.2)
	TG level: 127 mg/dL
	Soluble Interleukine-2 receptor: 8,730 U/mL
	PB smear: nonspecific finding
Case 2, HLH	BM study: hemophagocytes are occasionally seen; CD68: positive in increased histiocytes; CD8: focal positive in increased cytotoxic T cells
	Haptoglobin: 185.48 mg/dL [30–200]
	Serum ferritin: 6,218.8 ng/mL (23.9–336.2)
	TG level: 505 mg/dL
	Soluble Interleukine-2 receptor: 1,700 U/mL
	PB smear: nonspecific finding
	ADAMTS 13 activity: 87%
Case 3, TMA	BM study: no evidential finding of bone marrow involvement of hematologic malignancy
	EEG: abnormal awake and drowsy EEG, these features suggest moderate to severe diffuse cerebral dysfunction
	Haptoglobin: <10 mg/dL [30–200]
	Reticulocyte, percent/ absolute counts: 6.46 %, 179,600/μL
	PB smear: schistocyte 19–20/HPF
Case 4, TMA	Haptoglobin: <10 mg/dL [30–200]
	Reticulocyte, percent/ absolute counts: 5.10 %, 147,000/μL
	Serum ferritin: 5,487 ng/mL (23.9–336.2)
	PB smear: schistocyte 10/HPF
	ADAMTS 13 activity and Inhibitor: 6% and 0 BU/mL
Case 5, TMA	Haptoglobin: <10 mg/dL [30–200]
	Reticulocyte, percent/absolute counts: 9.93 %, 197,000/μL
	PB smear: schistocyte positive
	Serum ferritin: 1,621.1 ng/mL [23.9–336.2]
	ADAMTS 13 activity: 24%
	Brain MRI: no remarkable findings
Case 6, ischemic cholangiopathy	MRI: innumerable irregular small cystic lesions along the entire IHD; dilated IHD with multifocal stricture including the hilar portion without demonstrable mass lesion
	Liver biopsy: hepatocellular ballooning degeneration, microvesicular steatosis and intrahepatic cholestasis in zone 3; bile duct damage showing reactive change, proliferation and bile plugging; portal widening with acute inflammatory cell infiltration and periportal fibrosis; canalicular and intrahepatocytic cholestasis
	ERCP: both IHD dilatation and small filling defects; no CHD and CBD lesion
	Haptoglobin: 219.5 [30–200]
	PB smear: nonspecific finding
	ANA: negative
	Anti-ds DNA antibody: negative
	Anti-smooth muscle antibody: negative
	Anti-mitochondrial antibody: negative
Case 7, ischemic cholangiopathy	MRI: multifocal irregular beaded appearance of the IHD; no definitely visualized stones in IHD or CBD; irregular wall thickening and enhancement of both IHD; no abnormal lesion in the liver, pancreas and gall bladder
	Liver biopsy: cholestatic hepatitis showing ballooning degeneration, occasional acidophilic bodies and mild portal lymphocytic infiltration
	Serum ferritin: 1,745.9 ng/mL (23.9–336.2)
	PB smear: nonspecific finding
	ANA: negative
	Anti-ds DNA antibody: negative
	Anti-smooth muscle antibody: negative
	Anti-mitochondrial antibody: negative
	P-ANCA and C-ANCA: negative and negative
	Anti-LKM antibody: negative
Case 8, ischemic cholangiopathy	CT: multifocal dilatation of IHD without definite obstructive lesion; mild GB and periportal edema
	PB smear: nonspecific finding
	ANA: negative
	Anti-ds DNA antibody: negative
	P-ANCA and C-ANCA: negative and negative
	Anti-GBM antibody: negative
Case 9, ischemic cholangiopathy	MRI: irregular bead-like dilatation of intrahepatic bile ducts is in both lobes of liver, more prominent on the Lt. lobe; no evidence of obstructive lesion is in bile duct; no significant focal lesions in liver
	PB smear: non-specific finding
	ANA: negative
	Anti-smooth muscle antibody: negative
	Anti-mitochondrial antibody: negative
	Anti-cyclic citrullinated peptide antibody: negative
	P-ANCA and C-ANCA: negative and negative
	Anti-LKM antibody: negative

POD, postoperative day; TMA, thrombotic microangiopathy; BM, bone marrow; TG, triglyceride; PB, peripheral blood; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; EEG, electroencephalography; MRI, Magnetic resonance imaging; ERCP, endoscopic retrograde cholangiopancreatography; IHD, intrahepatic duct; CHD, common hepatic duct; CBD, common bile duct; ANA, antinuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; LKM, liver kidney microsomal; GBM, glomerular basement membrane.