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Medical Complications of Lung Transplantation

Moo Suk Park, M.D., Ph.D.

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

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Corresponding author
Moo Suk Park
Tel 82-2-2228-1955
Fax 82-2-393-6884
E-mail pms70@yuhs.ac
ORCID
https://orcid.org/0000-0003-0820-7615

Lung transplantation (LT) is now considered as an effective treatment option for end-stage lung diseases that improves the short and long-term survival rates and quality of life. As increasingly many LT procedures are being performed, the medical complications of LT are also increasing in frequency and emerging as a very important issue for transplant clinicians. Although chronic lung allograft dysfunction and infection are major causes of death after LT, many medical complications, several of which result from immunosuppressive treatment, contribute to increased mortality and morbidity. This article reviews the most frequent and important medical complications of LT, accompanied by a review of the literature and studies from South Korea, including lung allograft rejection, infection, and non-allograft organ systemic complications.

Keywords: Lung transplantation, Complications, Organ, Immunosuppression therapy, Infections, Graft rejection

Introduction

Lung transplantation (LT) is now considered as the standard treatment option for end-stage lung diseases. According to the International Society for Heart and Lung Transplantation (ISHLT) registry, more than 69,000 LT procedures have been performed worldwide [1]. The median survival after LT has substantially improved to 6.7 years because of advances in LT techniques and increasing experience with transplantation [1,2]. Although chronic lung allograft dysfunction (CLAD) and infection are major causes of death after LT, many medical complications also significantly influence morbidity and mortality after LT [1,2]. Appropriately managing these medical complications related to the risk of infection, malignancy, and drug toxicity—mainly caused by immunosuppressive therapy—will improve the survival rates of LT recipients (LTRs) [3].

This article concentrates on pulmonary and non-pulmonary organ-specific medical complications, which are mainly caused by immunosuppressive agents and have a significant influence on the short- and long-term management of LTRs [4-6], with a review of the literature and studies from South Korea.

Overview of organ system-related medical complications

The long-term use of calcineurin inhibitors (CNIs), corticosteroids, and other immunosuppressive agents may induce new chronic diseases or aggravate preexisting medical conditions, such as diabetes mellitus, hypertension, hyperlipidemia, cardiovascular diseases, and other medical diseases. Table 1 shows the most frequent medical complications after LT for various organ systems [4-6].

Pulmonary complications

Pulmonary infections

Infections are a major cause of death after LT. The long-term survival rates of LTRs remain poor because of CLAD and infections [7], as about 35% of LTRs still die within 1 year after LT [8]. Preventive antimicrobial prophylaxis is very important to reduce the incidence of bacterial, viral, and fungal infections after LT [7-11].

During the perioperative LT period, nosocomial and multidrug-resistant (MDR) pathogens induce infection in LTRs. Multiple types of infections occur in LTRs, although the lungs are the main site of infections. The risk factors

Table 1. Medical complications after lung complications according to organ systems [4-6]

Organ system	Most frequent complications	Incidence
Pulmonary	Rejection	30%–50% for 1 yr
	Infection	70% for 1 yr
	Thromboembolism	-
	Pleural effusion	-
	Drug toxicity	-
Cardiovascular	Hypertension	50% for 1 yr, 80% for 5 yr
	Atrial arrhythmia	25%–45%
	Coronary artery disease	-
	Acute pericarditis	-
Endocrine and metabolic	Diabetes mellitus	20%–43% for 1 yr, 33%–60% for 5 yr
	Hyperlipidemia	27% for 1 yr, 58% for 5 yr
	Hypomagnesemia	-
	Hyperkalemia	-
	Obesity	-
Renal	Acute kidney injury	50%–70%
	Chronic kidney disease	34% for 1 yr, 53% for 5 yr
	Electrolyte disturbances	-
Gastrointestinal and liver	Gastroesophageal reflux disease	65%
	Gastroparesis	24%
	Ileus	-
	Pneumatosis intestinalis	-
	Bowel ischemia and perforation	-
	Distal intestinal obstruction syndrome in cystic fibrosis	-
	Cholecystitis	-
	Diverticulitis	-
	Pancreatitis	-
	Nodular regenerative hyperplasia of the liver	-
Hematological	Cytopenia	-
	Immune hemolysis	-
	Thrombotic microangiopathy	-
	Venous thromboembolism/pulmonary thromboembolism	9%–64%/15%
Malignancies	Skin cancer	1.9% for 1 yr, 14.6% for 5 yr
	Post-transplant lymphoproliferative disorder	0.9% for 1 yr, 1.4% for 5 yr
	Bronchogenic carcinoma	-
	Other solid and hematologic malignancies	-
Neurologic (overall 45%–92%)	Tremors	-
	Seizure	-
	Cognitive dysfunction	-
	Posterior reversible encephalopathy syndrome	0.5%–5%
	Stroke	5%
	Progressive multifocal leukoencephalopathy	-
Musculoskeletal	Critical illness myopathy	
	Rhabdomyolysis	
	Avascular necrosis	3%–22%
	Osteoporosis	32%–54%
	Frailty	Fracture rate 6%–18%, BMD loss 4%–12%
Psychiatric	Delirium	
	Mood disorder and anxiety	30%
	Post-traumatic stress disorder	
Miscellaneous	Hyperammonemia	
	Hypogammaglobulinemia	

BMD, bone mineral density.

for infections are underlying medical conditions, altered anatomy, decreased cough function, history of MDR infection in the donor or recipient, nutritional status, surgical time, immunosuppressive therapy, and pathogens in the donor or recipient. Appropriate antibiotic prophylaxis in the perioperative period is standard for the management of LTRs after LT. A prompt diagnosis of infections and early initiation of therapy are critical for reducing the mortality caused by infections in LTRs [9].

Antimicrobial prophylaxis

Antimicrobial prophylaxis is needed for the prevention of several types of infections in LTRs; in particular, multidrug-resistant organisms (MDROs) have been associated with increased morbidity and mortality [7]. To prevent donor-derived nosocomial infections, antibiotic prophylaxis is used to target MDR pathogens. In particular, *Pneumocystis jiroveci* pneumonia (PCP) infections were reduced after universal prophylaxis with sulfamethoxazole/trimethoprim (TMP–SMX) compared to the rates of 5%–15% in non-prophylaxis patients within the first 6 months after LT [12].

Antifungal prophylaxis is also important to reduce invasive fungal infections (IFIs) after LT. The regimens include a systemic antifungal agent, inhaled amphotericin, or a combination thereof during 3 months to 1 year after LT [13].

There are 2 major strategies for cytomegalovirus (CMV) disease prevention after LT: preemptive therapy and antiviral prophylaxis. Antiviral prophylaxis for CMV is a standard aspect of management in LTRs. CMV is an important cause of morbidity and mortality in the first 6 months after LT. Oral valganciclovir and intravenous (IV) ganciclovir are generally used for CMV infection prophylaxis, after LT. As negative CMV immunity is the most important risk factor for CMV disease after LT, international guidelines recommend 6 to 12 months of prophylaxis in CMV-seronegative recipients with CMV-seropositive donors and 3 months of prophylaxis for CMV-seropositive recipients [14,15]. Acyclovir or valacyclovir is applied for antiviral prophylaxis against herpes simplex virus and varicella-zoster virus after solid organ transplantation (SOT) [16,17].

Donor-derived bacterial infections

Perioperative antibiotic therapy is administrated to target colonized pathogens in recipients before transplantation [18]. The donor's pre-transplant flora is very important, and respiratory samples via bronchoscopy showed that bacterial transmission from donor to recipient occurred in 48%–89% of LTRs [19]. Culture studies for the donor and recipient microbial flora of the lung before LT may be helpful for targeting antimicrobial prophylaxis after LT. Sixty percent of the transmitted infections were bacterial or viral, while the others were fungal, parasitic, and mycobacterial [19]. Most donor-transmitted infections occurred within 30 days after LT [20]. As donor-derived infections are associated with high mortality after LT, a careful evaluation of the donor and laboratory testing for specific targets are necessary to prevent the transmission of donor infections [21].

Bacterial infections

The incidence of bacterial infections is very high, accounting for up to 50% of all infectious diseases in LTRs. Infection from the donor, chronic colonization in LTRs, or MDROs from the intensive care unit (ICU) may cause early bacterial infections after LT (Fig. 1). Medical comorbidities and the severity of the recipient's condition, airway abnormalities after surgery, decreased mucociliary clearance and cough reflex, impaired immunity and lymphatic drainage, necrosis of the bronchial anastomosis, and exposure to the environment are associated with early bacterial infection in LTRs [7,22]. Prompt diagnosis and early treatment are critical in the management of bacterial infections. As soon as a possible infectious workup is performed, including multiple sites that could be sources of infection (e.g., blood, sputum, effusions, and urine for bacterial cultures), empiric antibiotics should be started [23]. The respiratory tract is the most frequent bacterial infection site in LTRs, and bronchoscopy is helpful to identify causes of pneumonia [24].

In a South Korean report, high levels of preexisting MDROs in the donor were transmitted to lung allografts, but this was not associated with early bacterial pneumonia or mortality in LTRs [25]. However, severe thrombocytopenia, acute kidney injury (AKI), and MDR *Acinetobacter baumannii* infection were related to 90-day mortality [26]. In addition, early post-LT carbapenemase-producing Enterobacteriaceae (CPE) acquisition may increase the risk of bronchial dehiscence and be an independent risk factor for poor clinical outcomes in LTRs [27,28]. Careful screening and management for CPE during the early post-LT period are necessary in recipients with risk factors.

Fishman [29] and Fishman and Rubin [30] described the etiological timeline of infections, an understanding of which improves the prophylaxis and empirical treatment of infections in SOTs as follows: first, nosocomial and donor-derived infections; second, opportunistic infections;

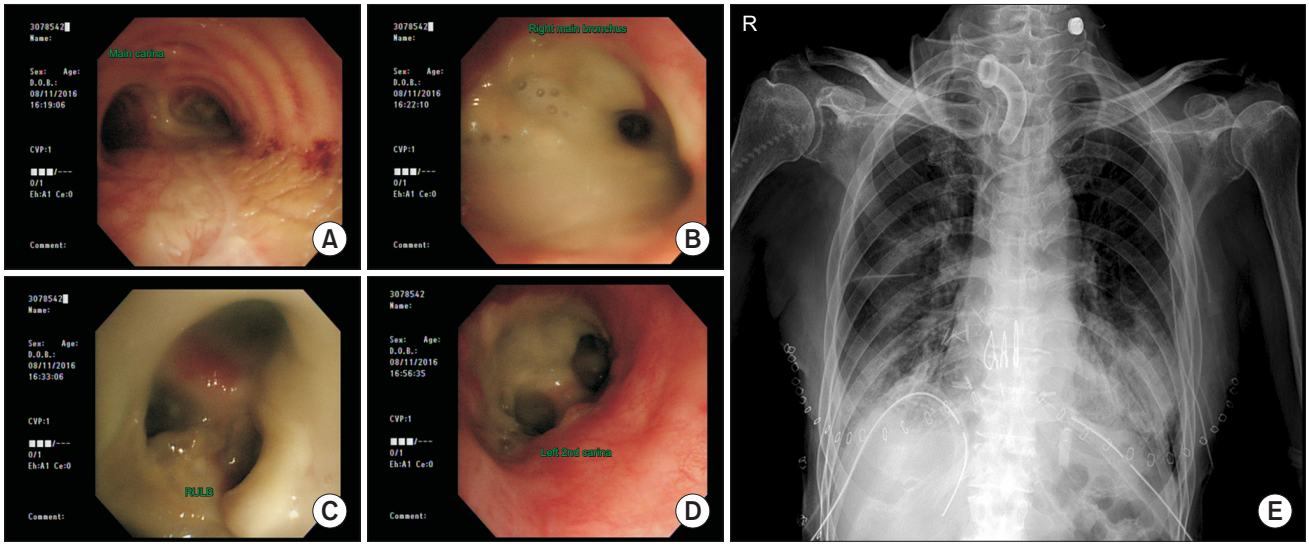

Fig. 1. A 65-year-old male patient with idiopathic pulmonary fibrosis with transmitted donor multidrug-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae* in pre-donation culture by bronchoscopy. (A–D) Bronchoscopic findings and (E) chest X-ray showed pneumonia in both lower lobes. RULB, right upper lobe bronchus.

and last, community-acquired infections. In contrast, a South Korean report showed that although the frequency of respiratory infections decreased sharply in the late post-LT period, Gram-negative MDR bacteria were the most common pathogens [31].

Viral infections

Viral infections account for up to 30% of all infectious complications in LTRs and affect organ graft function and the immune system [32]. A South Korean study suggested that lymphopenia and high doses of steroids were associated with CMV reactivation in LTRs. In addition, repetitive CMV reactivation could be related to development of chronic kidney disease (CKD) and pneumonia [33]. CMV presents as pneumonitis, CMV viral syndrome, and gastrointestinal (GI) symptoms. The diagnosis of CMV relies on different types of tests, targeting antibodies against CMV, CMV proteins, or CMV DNA. Antiviral therapy with oral valganciclovir or IV ganciclovir is the first choice for both prophylaxis and treatment of active CMV disease. Antiviral treatment of CMV should be maintained until a negative CMV viral load on 2 consecutive tests and improvement in symptoms, which need to be closely monitored. When CMV resistance is detected, IV foscarnet or cidofovir may be used [34]. The implementation of universal preventive antiviral prophylaxis against CMV, vaccination for influenza, and early antiviral treatment have reduced viral infections and improved the survival and quality of life in LTRs [11].

After the first year post-LT, community-acquired respiratory viruses cause viral infections in LTRs, influencing their long-term outcomes. Oral ribavirin for the treatment of parainfluenza, respiratory syncytial virus, or human metapneumovirus and cidofovir for adenovirus have been used [35].

Post-transplant lymphoproliferative disorder (PTLD) is well known and related to Epstein-Barr virus (EBV)-associated malignancy after SOT. The incidence of PTLD caused by EBV is high, reaching up to 30% in LTRs. Monitoring the EBV viral load via blood polymerase chain reaction (PCR) tests enables the earlier detection of PTLD. Acyclovir or ganciclovir is used for prophylaxis of high-risk patients with EBV-seropositive donors [36].

Severe acute respiratory syndrome coronavirus 2 infection is very closely associated with mortality in LTRs. Most coronavirus disease 2019 infections in LTRs were highly severe, and the mortality rate was up to 40% [37,38].

Fungal infections

IFIs more frequently develop in LTRs than in other SOT recipients. Airway abnormalities after surgery, exposure of the allograft to fungi in the environment, decreased mucociliary defenses, the diminished cough reflex, and impaired immunity due to immunosuppressive therapy are closely related to IFI in LTRs [39]. The incidence of IFIs is 3%–19% within the first year after LT. IFIs can cause tracheobronchial infections at anastomotic sites, as well as invasive pulmonary and disseminated infections (Figs. 2, 3). The

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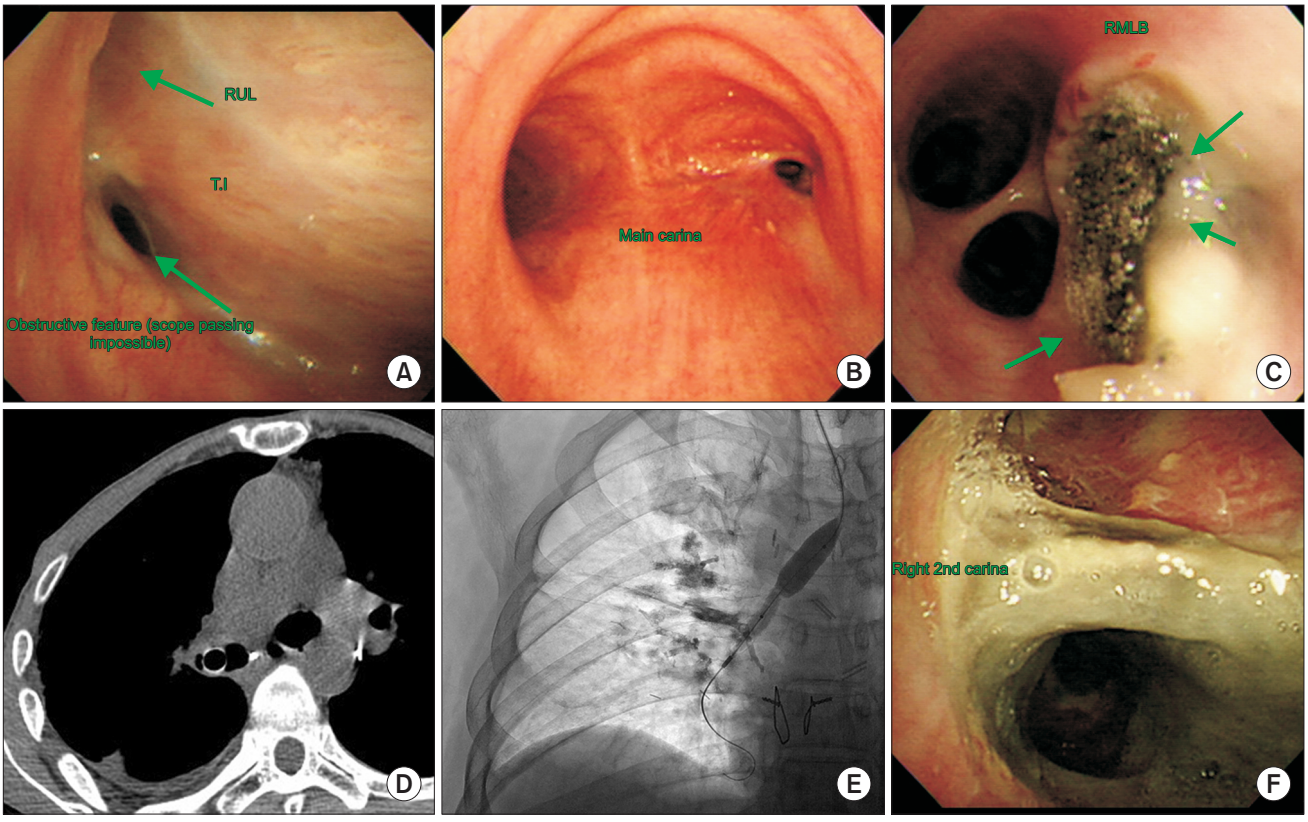

Fig. 2. (A–F) Multiple cases of airway stenosis after *Aspergillus* and bacterial tracheobronchitis infection (arrows). RUL, right upper lobe; RMLB, right middle lobe bronchus; T.I, truncus intermedius.

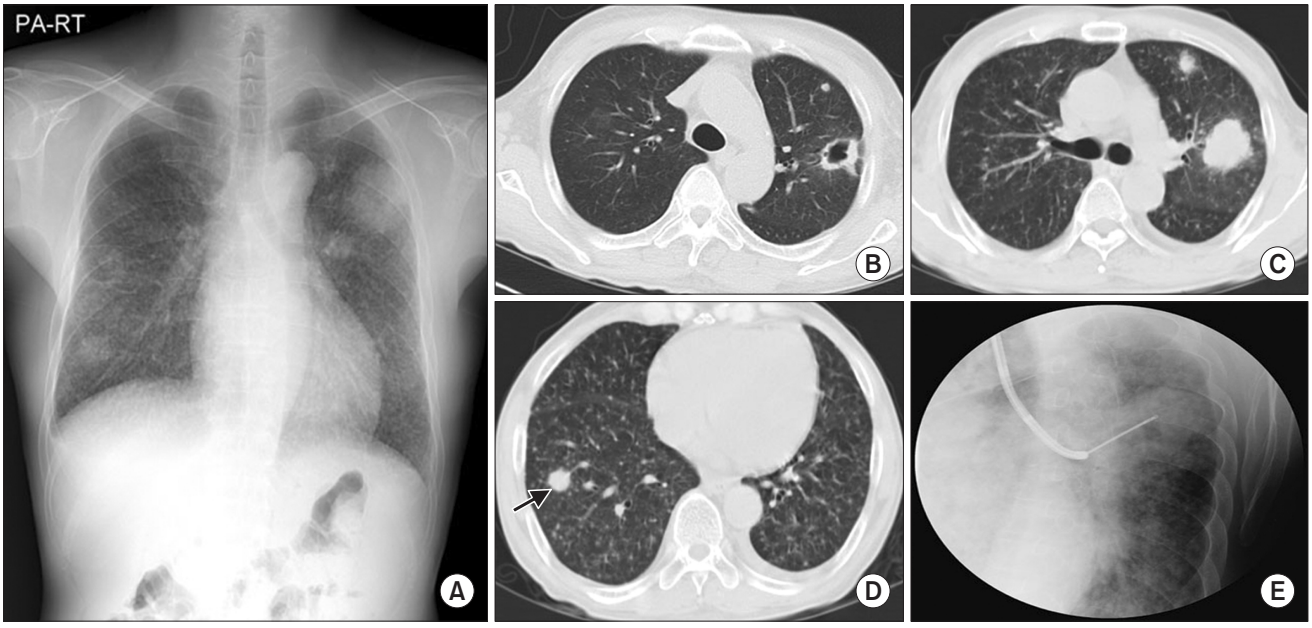

Fig. 3. (A–E) Invasive pulmonary *Aspergillus* infection confirmed by transbronchial lung biopsy (arrow). PA, posterior-anterior; RT, right.

risk of mortality is low, but bronchial stenosis and wound dehiscence frequently occur in tracheobronchitis, which refers to a semi-invasive and potentially invasive airway infection within the first 3 months post-LT caused by ischemic injury after surgery and disruption of the airway epithelium. IFIs and disseminated infections after LT are major contributors to mortality in LTRs, as they cause 40% and 80% of deaths, respectively [40,41].

The most common etiological agents of IFIs among LTRs are *Aspergillus* (44%), followed by *Candida* (23%) spp. Other fungal infections are present in fewer than 4% of cases [42]. In the early period, within 1 month after LT, *Candida* infection more commonly presents as candidemia due to indwelling catheter infections and pulmonary infections [41].

Aspergillus colonization of the lung is associated with frequent *Aspergillus* infection, with an incidence of 23%. The cumulative incidence of mold colonization is 20%–50% of LTRs [43].

A definitive diagnosis of IFI requires histopathologic evidence of tissue invasion and the identification of fungal culture in a respiratory specimen [44]. In addition, laboratory evidence of fungal infection, signs or symptoms of infection, and characteristic findings of chest computed tomography (CT), such as multiple pulmonary consolidations, nodules, or cavities. Bronchoalveolar lavage fluid (BALF) galactomannan (GM) testing is widely used and has a higher diagnostic value, with a sensitivity of 60%–82% in SOT recipients, than serum GM, which is limited by its low sensitivity. A BALF GM test should be included in the pneumonia workup [45,46]. A South Korean report showed that fungus-positive cultures in respiratory samples were present at a higher rate in the first 3 months after LT than subsequently, and the predominant fungal organism was *Candida* spp. rather than *Aspergillus* spp. The risk factors for developing a fungal infection after LT were old age, underlying connective tissue disease-associated interstitial lung disease, the use of antifungal agents before LT, and a longer hospital stay after LT. IFIs and antifungal treatment failure significantly increased overall mortality [47]. Bronchoscopic surveillance and biopsy, prompt fungus culture, and the appropriate use of antifungal agents are the most important aspects of the management of fungal infections in the first year after LT (Fig. 3). The treatment of fungal infections after LT is based on the specific fungal pathogen being targeted [48].

Other infections

Hyperammonemia is rare, but toxic to the brain, and induces encephalopathy with mental changes, cerebral edema, and fatal damage to the brain after the early period of LT. Enzyme deficiency (e.g., a relative lack of ornithine transcarbamoylase from the urea cycle), pulmonary hypertension, a history of liver disease, the use of CNIs, and AKI are associated with hyperammonemia, which has an incidence of about 1% after LT [49]. *Mycoplasma hominis* or *Ureaplasma urealyticum* infections sometimes induce hyperammonemia in LTRs [49,50]. A PCR analysis should be considered to detect these urea-splitting infections, which can be treated with azithromycin or fluoroquinolone [50]. Patients should be monitored for a rise in ammonia levels in the early period after LT. Early detection and prompt hemodialysis are crucial in the management of hyperammonemia.

Mycobacterial infections have been reported rarely, but *Mycobacterium tuberculosis* (MTB) and non-tuberculous mycobacteria (NTM) infections occur in a relatively high proportion of LTRs (about 4%) (Figs. 4, 5) [51]. In countries

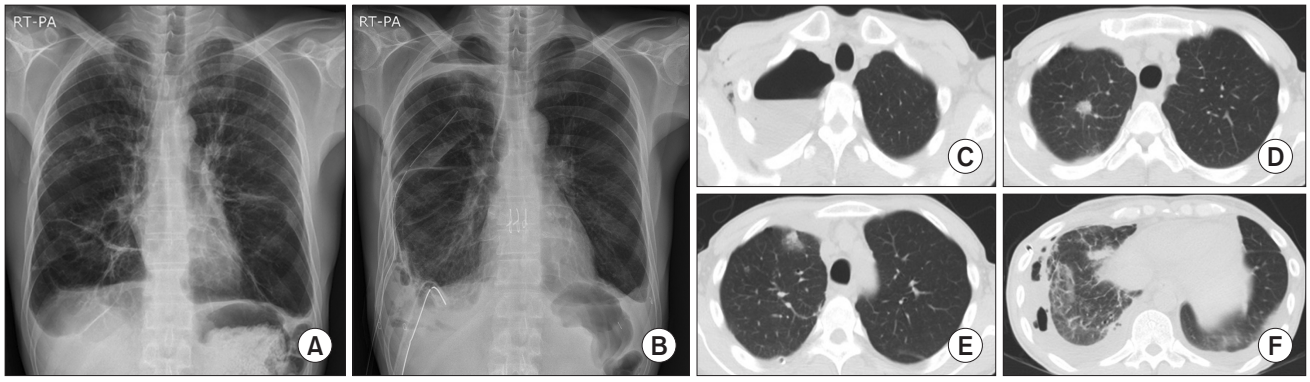

Fig. 4. (A–F) A 49-year-old male patient who underwent lung transplantation due to graft-versus-host disease after hematopoietic stem cell transplantation. A 1-month post-lung transplantation sputum culture showed *Mycobacterium tuberculosis* from the donor. PA, posterior-anterior; RT, right.

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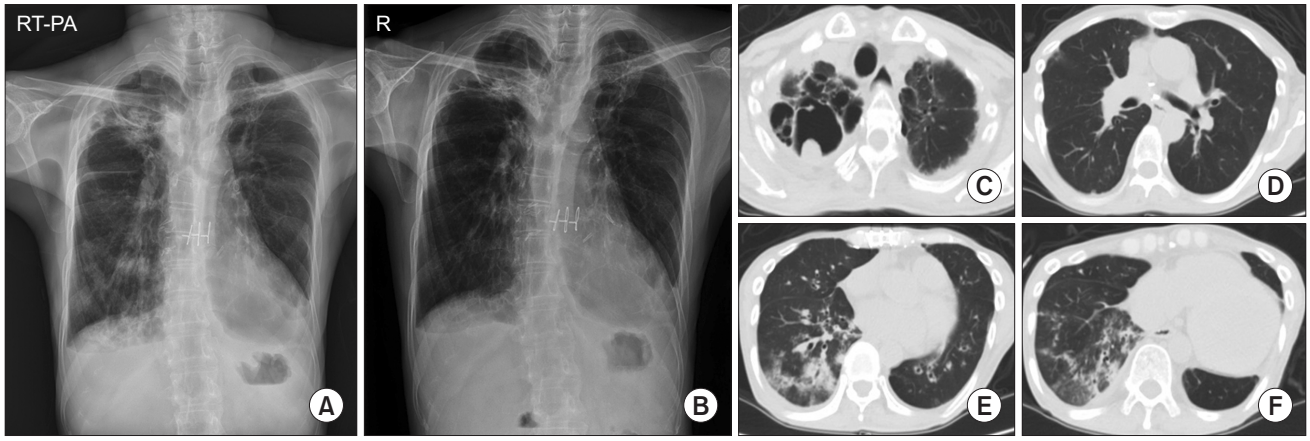

Fig. 5. (A–F) A 62-year-old male patient who underwent lung transplantation due to chronic bronchiectasis and cor pulmonale. Five years after lung transplantation, mixed-type chronic lung allograft dysfunction with airway obstructive bronchiolitis obliterans syndrome and restrictive allograft syndrome in both upper lobes developed, and sputum culture showed non-tuberculous mycobacteria (*Mycobacterium intracellulare*). PA, posterior-anterior; RT, right.

where MTB is endemic, disease most often occurs from the reactivation of a latent tuberculosis infection. Underlying structural lung diseases in the pre-transplant or perioperative period with colonization, the development of structural lung disease secondary to bronchiolitis obliterans syndrome (BOS) after LT, and a transmitted infection derived from the donor are associated with new or re-infection with MTB and NTM after LT [51]. *M. avium* complex (MAC) and *M. abscessus* can induce infection. NTM infections, particularly *M. abscessus*, should be further evaluated and treated before LT. A South Korean report showed that the prevalence of NTM infection after LT was 6.5%. The highest proportion (4.2% of patients) had *M. abscessus* infections, followed by MAC pulmonary disease. These NTM infections did not influence mortality after LT [52].

Nocardia infections after LT are rare, but related to increased mortality. *Nocardia farcinica* is more likely to cause central nervous system infections than other species (Fig. 6). Husain et al. [53] showed that the incidence ranged from 0.6% to 2.1% of LTRs, and the mortality rate was 40%. PCP prophylaxis with low-dose TMP–SMX does not prevent nocardiosis. If nocardiosis is suspected, appropriate media with longer incubation periods and antimicrobial susceptibility testing should be applied [53].

Lung allograft rejection

Rejection is a major complication after LT (Fig. 7). Graft failure or rejection is a common early cause of death within 1 year after LT, accounting for approximately 22.7% of deaths. CLAD is the most common cause of death within I year after LT [54]. External exposure and infection increase the risk of rejection after LT [55]. Acute rejection can be mediated by either acute cellular rejection (ACR) involving T cells or antibody-mediated rejection (AMR) involving B cells. Because acute rejection is also a risk factor for CLAD, detection and treatment are important. The diagnosis of acute rejection is made by a combination of a lung function decrease by more than 10%, chest imaging, and the presence of perivascular and interstitial lymphocyte infiltrates through transbronchial lung biopsy [56]. The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of high-resolution CT scans in acute rejection were 50%, 97.5%, 80%, 90.1%, and 89.6% in a South Korean study [57].

The ISHLT Pathology Council Working Group revised the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection after LT in 2007 [58]. ACR is most commonly diagnosed in the first 3 to 6 months, and within the first 1 to 2 years after LT [59]. Anti-human leukocyte antigen antibodies and CMV infection are associated with ACR after LT [60]. The presence of donor-specific antibodies (DSAs) is also a risk factor for ACR and AMR [61]. A South Korean study showed that the mean fluorescence intensity (MFI) was relatively high in LTRs with DSA and high-grade primary graft dysfunction (PGD) [62]. Preoperative DSAs and panel-reactive antibodies are associated with worse outcomes after LT [63]. Therefore, recipients with high MFI with or without DSAs before LT need to be closely monitored. In a South Korean crossmatching study, 9 patients (4.1%) showed T cell- and/or B cell-positive crossmatches among 208 patients of com-

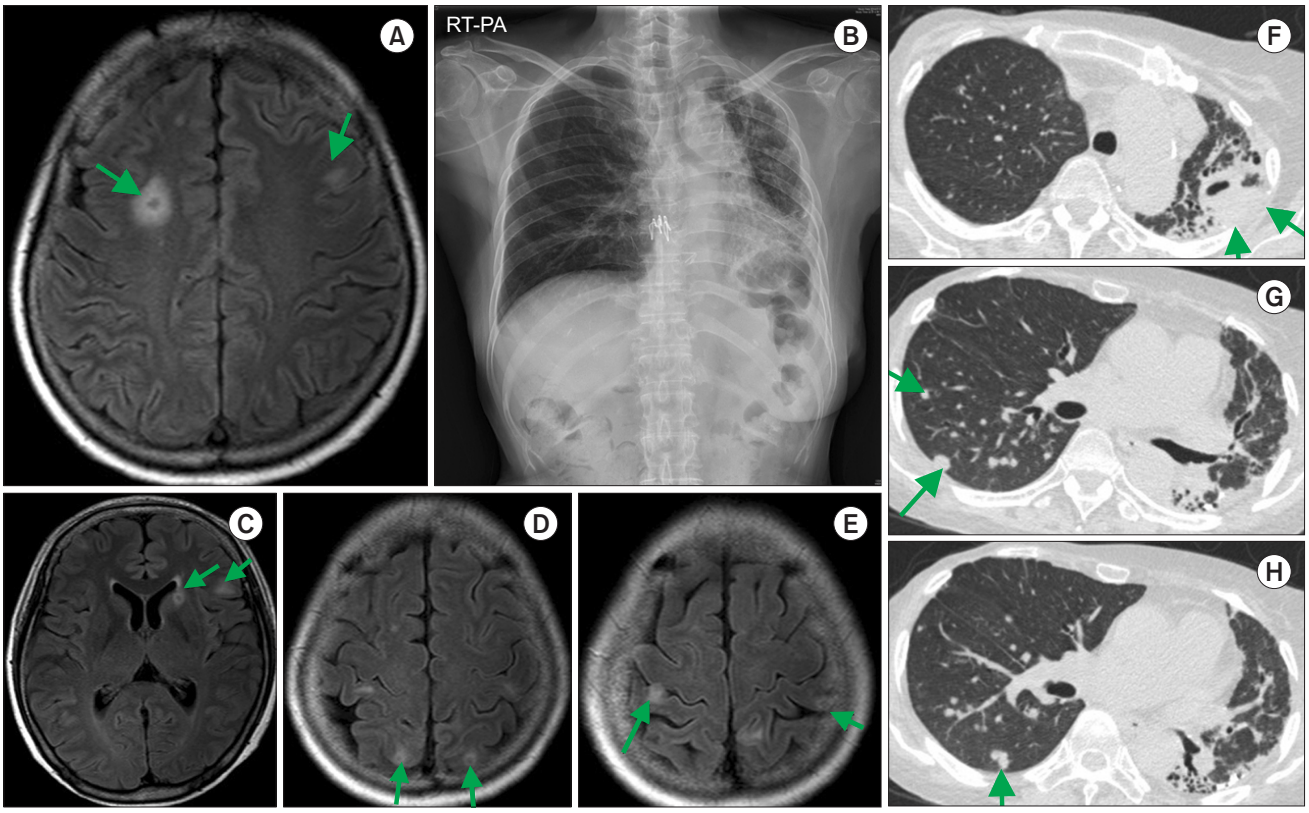

Fig. 6. (A–H) A 64-year-old female patient who underwent single lung transplantation due to idiopathic pulmonary fibrosis. Four months post-lung transplantation, *Nocardia farcina* infection developed in the lung and brain through a leg wound (arrows). PA, posterior-anterior; RT, right.

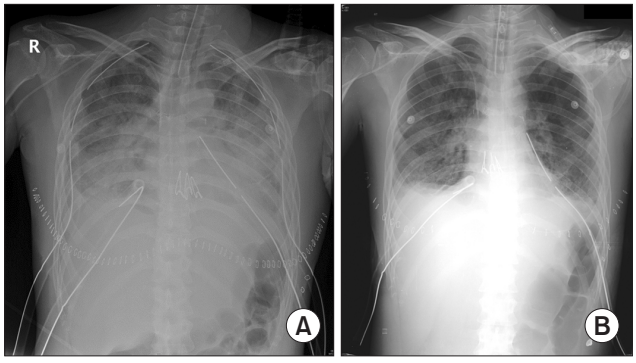

Fig. 7. A 34-year-old male patient who underwent bilateral lung transplantation due to idiopathic pulmonary fibrosis. (A) At 5 days post-transplant, fever, low prograft level, pulmonary edema, and hypoxemia developed, and bronchoalveolar lavage fluid analysis showed a total of 531 cells with 8% of polynuclear neutrophils and (B) improved acute rejection after methylprednisolone (500 mg) pulse infusion for 3 days and slow tapering from prednisolone.

plement-dependent cytotoxic crossmatch, and 125 had flow cytometric crossmatch. The incidence of PGD, acute rejection, and CLAD was not increased in positive LTRs. However, 1-year survival after LT was poor in positively crossmatched LTRs [64].

In general, the management of asymptomatic minimal acute rejection grade A1 remains a matter of debate, but ACR grades A2 or higher require treatment with methylprednisolone (10–15 mg/kg daily, or 500 to 1,000 mg, for 3 days) followed by tapering with oral prednisolone. There is no accepted, standardized regimen for the treatment of persistent or refractory acute rejection, but additional therapies have been tried, including antithymocyte globulin, alemtuzumab, total lymphoid radiation, and extracorporeal photopheresis [65].

The ISHLT published a consensus document on the standard diagnosis of AMR in 2016, with a division of AMR into clinical and subclinical AMR according to allograft function [66]. AMR is further defined by the following criteria: (1) exclusion of other potential causes such as infection; (2) abnormal histopathologic features; (3) the presence of circulating DSAs; and (4) positive C4d staining in the capillary endothelium [66].

The optimal treatment of AMR is not well known. AMR

treatment targeting B-cell pathway suppression and depleting circulating antibodies such as IV immunoglobulin, plasmapheresis, rituximab, and eculizumab, alone or in combination, have been tried, but the outcomes have been poor despite aggressive treatment [66].

Cardiovascular and metabolic complications

Cardiovascular comorbidities such as hypertension, hyperlipidemia, and diabetes are very common after LT, but surprisingly, mortality due to cardiovascular disease occurs in fewer than 5.3% of LTRs [67].

Diabetes mellitus

Post-transplant diabetes mellitus (PTDM) is a common and potentially serious complication after LT. PTDM has been developed after LT in 20%–40% of LTRs within 1 year after LT [8]. Combinations of CNIs and glucocorticoids for immunosuppressive therapy are well-known risk factors for the development of PTDM [67]. The early detection of PTDM and care regarding risk factors are key to its management [68,69].

Insulin treatment is needed in the early post-transplant phase, accompanied by a high dose of immunosuppressive therapy, and exerts a prohibitive effect on the development of PTDM [70]. Persistent hyperglycemia (≥180 mg/dL) indicates the need to start insulin treatment and lifestyle modifications [69]. After LT, hypomagnesemia is common and is related to the development of PTDM in LTRs [71]; therefore, magnesium supplementation may be beneficial.

Hypertension

Hypertension has been reported to occur in 50% of LTRs after 1 year and 80% after 5 years post-LT [72]. The risk factors are similar to those of PTDM, including old age, overweight, an unhealthy diet, excessive dietary sodium, insufficient physical activity, consumption of alcohol, family history, and the use of CNIs and corticosteroids.

In the early perioperative period, volume overload from IV fluid administration is common and frequently contributes to hypertension. Immunosuppressive medications, such as CNIs and corticosteroids, are associated with post-LT hypertension. AKIs commonly develop, in approximately 50% of patients in the early period post-LT, and contribute to the development of hypertension. Fluid control, diuretics, and beta-blockers are commonly used to control hypertension [73,74]. Reliable blood pressure (BP) measurements are mandatory in LTRs. A reasonable BP target in LTRs is less than 130/80 mm Hg. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are usually avoided due to AKI and the potential to induce hyperkalemia.

Calcium channel blockers (CCBs), which are also used to control post-LT hypertension induced by CNIs, can cause vascular vasoconstriction via mineralocorticoid receptors in the smooth muscle [75]. Therefore, CCBs seem to be appropriate antihypertensive medications for post-transplant hypertension, but it is necessary to consider interactions between CCBs and other drugs, including CNIs, statins, and antifungal azoles. The development of toxicity should be monitored and managed by dose reduction [76].

Hyperlipidemia

Hyperlipidemia is a well-recognized complication of LT. Hyperlipidemia has been reported to occur in 27% of LTRs at 1 year and in 58% at 5 years [72]. Its risk factors include old age, male sex, diabetes, prednisone dose, obesity, antihypertensive therapy, and use of CNIs and corticosteroids. A low-fat diet and cholesterol-lowering agents, including statins and fibrates, are the most common treatments, but may require dose reduction due to possible drug interactions with immunosuppressive medications [77]. The risk of rhabdomyolysis may be increased with the concomitant use of statins, fibrates, and CNIs. Regarding hypertriglyceridemia, current guidelines recommend starting the use of hydroxymethylglutaryl coenzyme-A reductase inhibitors (i.e., statins) and modifying the risk factors in patients with an atherosclerotic cardiovascular disease risk more than 7.5%. Persistent hyperlipidemia should be aggressively treated to prevent cardiac events.

Atrial arrhythmia

Atrial arrhythmias (AAs), such as atrial fibrillation, atrial flutter, and atrial tachycardia, are common in the early postoperative phase after LT, occurring in 25% to 45% of patients [78-80]. A South Korean study showed that post-LT AAs occurred in 46 (30%) of 153 consecutive LTRs. Preoperative higher right atrial pressure and longer mechanical ventilation were independent risk factors for AAs, which were associated with worse outcomes after LT [80].

Renal complications

Acute kidney injury

Post-transplant AKI is a very common complication after LT; it has been reported to occur in 30%–70% of LTRs and is associated with higher mortality and morbidity [74,81]. Multifactorial risk factors contribute to the development of AKI, including advanced age, preoperative severe end-stage lung disease status of the recipient, blood loss and hemodynamic instability, the use of preoperative mechanical ventilation or extracorporeal membrane oxygenation (ECMO), single or double LT type, operation time, and exposure to nephrotoxic agents such as CNIs and antimicrobial drugs in the perioperative period [82,83].

AKI is associated with a longer duration of mechanical ventilation and hospital stays; furthermore, it increases the risk of CKD, hypertension, and mortality in LTRs [82,83]. In a 2019 report from the ISHLT, the prevalence of severe AKI and chronic dialysis was 4.8% and 3.4% at 1 year post-transplantation [8], and these factors were associated with increased mortality [84]. A South Korean study showed that 59 patients (39.8%) developed AKI within 1 month after LT among 148 LTRs. Stage I or II AKI was present in 26 patients (17.5%), and stage III AKI was found in 33 (22.2%). The risk factors for AKI development were preoperative anemia, the amount of red blood cells transfused, and the use of colistin infusion. AKI was closely related to increased mortality in the postoperative period and 1-year mortality after LT [85].

These studies have implications for detecting at-risk patients and preventing AKI before LT and during the perioperative period according to the pretransplant risk factors and surgical procedures. It is crucial to screen and monitor patients with these risk factors. A balanced volume and fluid management strategy is essential for adequate renal perfusion and preventing the development of AKI. Close monitoring of urine output and creatinine levels may be helpful in reducing the development of AKI. Higher CNI concentration levels are related to AKI, and intensive and careful monitoring of the CNI trough level is essential in LTRs. Induction therapy with basiliximab may delay the use of CNIs, such as tacrolimus or cyclosporin, and help to reduce the development of AKI in patients at high risk [86].

Chronic kidney disease

AKI in the early post-LT period is closely related to a higher occurrence of CKD [74,87]. In a recent report, CKD occurred in 27% and 58% of LTRs at 1 and 5 years after LT, respectively [88]. Preoperative and postoperative hypertension, as well as the use of CNIs, is closely related to the development of CKD and end-stage renal disease (ESRD) [88,89]. The prevention of AKI and intense management of other risk factors are crucial for the prevention of CKD. Early hypertension and hyperlipidemia management after LT is also important to prevent CKD development and progression to ESRD. Immunosuppression adjustment is essential for managing CKD with the support of nephrologists. In addition, avoidance of nephrotoxic medications and the use of alternative immunosuppressive agents should be considered [90].

Gastrointestinal complications

Long-term GI complications due to immunosuppressive agents are common in LTRs. In the early post-transplant period, ileus and colonic perforation are common GI complications that could be fatal [91]. Gastroesophageal reflux

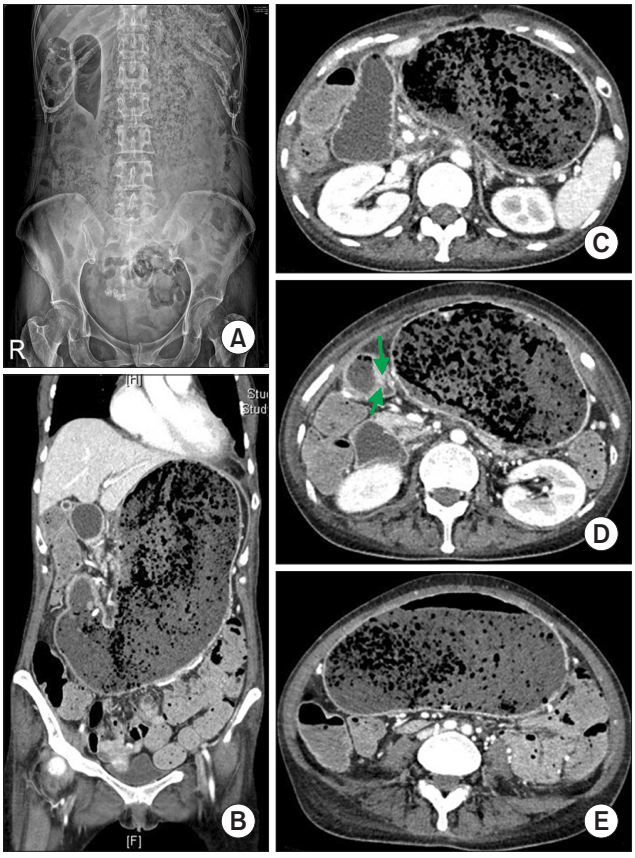

Fig. 8. (A–E) Severe gastroparesis and superior mesenteric artery syndrome requiring decompressive surgery (arrows).

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disease (GERD), nausea, diarrhea, constipation, and abdominal pain are common after LT [3,91]. Gastroparesis occurs in about 24% of LTRs, if refractory nausea is sustained, gastroparesis should be excluded (Fig. 8), Promotility drugs sometimes improve gastroparesis [92]. In a meta-analysis, serious GI complications such as colitis, pancreatitis, cholecystitis, diverticulitis, CMV infection, bowel obstruction, and peptic ulcer disease occurred in about 20% of LTRs. The proportion of patients requiring a surgical intervention is estimated to be between 9.6% and 12.5% [91,93].

Multiple studies have shown that GERD and delayed gastric emptying worsen allograft function and mortality [94]. Vagal nerve dysfunction, immunosuppressive agents, and lower esophageal sphincter function are associated with a high prevalence of GERD. Proton pump inhibitors or H2 blockers are used for symptomatic relief as anti-reflux agents. Promotility agents may also be used to improve gastric motility. Early anti-reflux surgical intervention (ARS) has been shown to stabilize or improve lung function in some patients with BOS and has been demonstrated to be safe [94]. With the high prevalence of GERD and the benefits of ARS, screening for GERD could be suggested.

Peptic ulcer disease and esophageal diseases can induce GI hemorrhage, which should be evaluated immediately. As ischemic or CMV colitis, colorectal ulcer, and PTLD can cause hematochezia or melena, a prompt evaluation is necessary [91]. Gastric ulcer perforation and hyperbilirubinemia due to secondary sclerosing cholangitis were reported in South Korean studies [95-97].

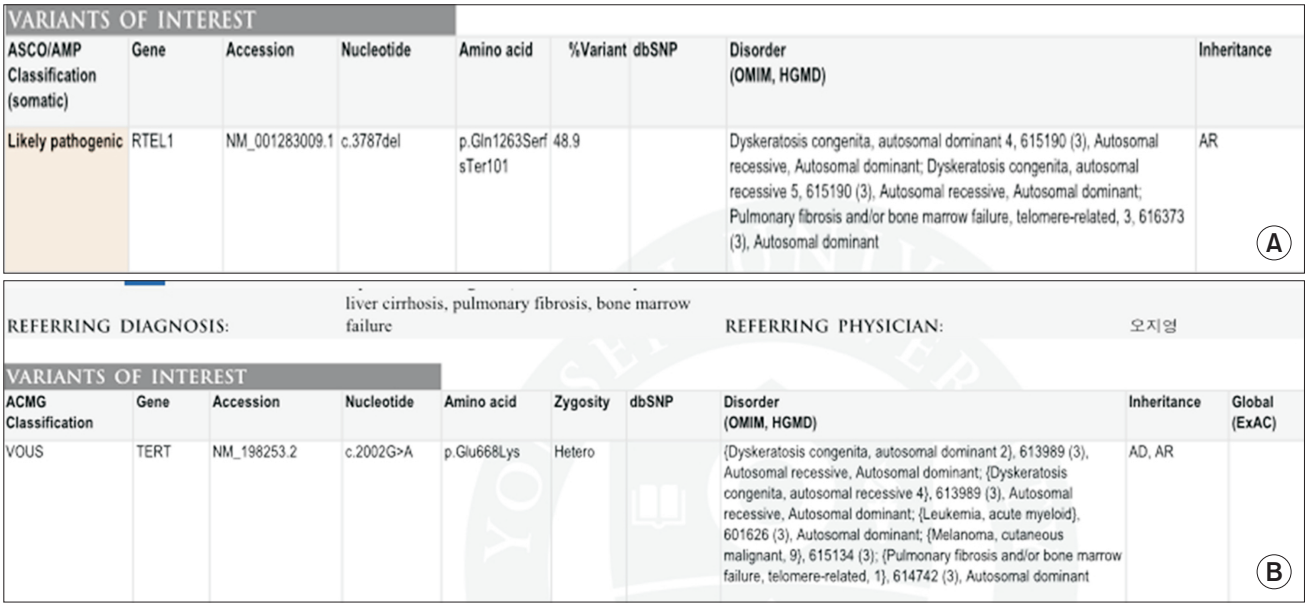
Hematologic complications

Cytopenia and anemia

The most common hematologic complication is cytopenia, which is induced by the use of immunosuppressive agents and antibiotics. It is important to exclude other etiologies of cytopenia, such as viral infections or iron deficiency [98]. Colony-stimulating factor use may help increase the neutrophil count, but may also be associated with rejection [99].

Thrombotic microangiopathy and microangiopathic hemolytic anemia

CNIs have been related to thrombotic microangiopathy with hemolytic anemia manifesting as hemolytic uremic syndrome or thrombotic thrombocytopenic purpura [100]. CNIs, CMV, or other viral infections and graft rejection are risk factors for endothelial damage. Discontinuation of these drugs or changing to alternative drugs is the most important treatment. Plasmapheresis and high-dose corticosteroids are often tried, but their benefit is unclear in transplant-associated thrombotic microangiopathy [101, 102].



VARIANTS OF INTEREST

ASCO/AMP Classification (somatic)	Gene	Accession	Nucleotide	Amino acid	%Variant	dbSNP	Disorder (OMIM, HGMD)	Inheritance
Likely pathogenic	RTEL1	NM_001283009.1	c.3787del	p.Gln1263Serf sTer101	48.9		Dyskeratosis congenita, autosomal dominant 4, 615190 (3), Autosomal recessive, Autosomal dominant; Dyskeratosis congenita, autosomal recessive 5, 615190 (3), Autosomal recessive, Autosomal dominant; Pulmonary fibrosis and/or bone marrow failure, telomere-related, 3, 616373 (3), Autosomal dominant	AR

A

REFERRING DIAGNOSIS: liver cirrhosis, pulmonary fibrosis, bone marrow failure

REFERRING PHYSICIAN: 오지영

VARIANTS OF INTEREST

ACMG Classification	Gene	Accession	Nucleotide	Amino acid	Zygosity	dbSNP	Disorder (OMIM, HGMD)	Inheritance	Global (ExAC)
VOUS	TERT	NM_198253.2	c.2002G>A	p.Glu668Lys	Hetero		{Dyskeratosis congenita, autosomal dominant 2}, 613989 (3), Autosomal recessive, Autosomal dominant; {Dyskeratosis congenita, autosomal recessive 4}, 613989 (3), Autosomal recessive, Autosomal dominant; {Leukemia, acute myeloid}, 601626 (3), Autosomal dominant; {Melanoma, cutaneous malignant, 9}, 615134 (3); {Pulmonary fibrosis and/or bone marrow failure, telomere-related, 1}, 614742 (3), Autosomal dominant	AD, AR	

B

Fig. 9. (A, B) Two cases of suspected short telomere syndrome combined with pulmonary fibrosis, liver diseases, bone marrow suppression, and frequent infection; the diagnosis was confirmed by next-generation sequencing.

Short telomere syndromes

Telomerase-related mutations are a specific etiology of cytopenia. The clinical features of short telomere syndromes are pulmonary fibrosis, bone marrow and liver failure, frequent infections, and a family history of these diseases (Fig. 9) [103]. Age-adjusted telomere length less than the 10th percentile was related to worse outcomes at 5 years after LT [104].

Venous thromboembolism

Venous thromboembolism (VTE) frequently occurs in the early period and has been associated with worse outcomes after LT. The incidence of VTE has been reported to be 10%–60%. VTE mainly develops from deep venous thromboses in the lower legs, although pulmonary embolism (PE) occurs in up to 15% of cases (Fig. 10) [105]. The known risk factors for VTE after LT include a hypercoagulable state, older age, diabetes mellitus, pneumonia, use of cardiopulmonary bypass (CPB) or ECMO, interruption of VTE prophylaxis, multiple central venous catheters, and cumulative ICU days [105,106]. Because the dual blood supply from the bronchial artery is absent after LT, PE can cause pulmonary infarction. Heparin infusion followed by warfarin or new oral anticoagulants for long-term anticoagulation is standard treatment. A standardized thromboprophylaxis protocol for VTE or PE is essential [107].

Neurologic complications

Neurologic complications are also common, with a wide range of incidence (approximately 40%–90%) during 10 years after LT in some studies [108,109]. Major neurologic complications occur in approximately 9% of patients within 2 weeks after LT [108]. Smith et al. [109] reported that postoperative delirium and posterior reversible encephalopathy syndrome (PRES) due to neurotoxicity were the most common neurologic complication in the early period after LT. Stroke, seizure, and encephalopathy were also common within the first year after LT [108]. Age, longer use of CPB or ECMO, the development of AKI, and severe PGD are risk factors [108,109]. Neurotoxicity from immunosuppressive agents is also an important factor in LTRs receiving CNIs and azathioprine. Neurologic complications are associated with worse outcomes, especially in the early period after LT [108,109].

Stroke

LTRs are at higher risk for stroke, with particular etiologies including an embolism from the heart and pulmonary vessels during surgery [110]. LTRs may be vulnerable to early neurologic complications due to chronic hypoxemia and ischemic injury from hemodynamic instability during the operation [108]. In addition, the development of AA poses a high risk for cardiovascular thromboembolic

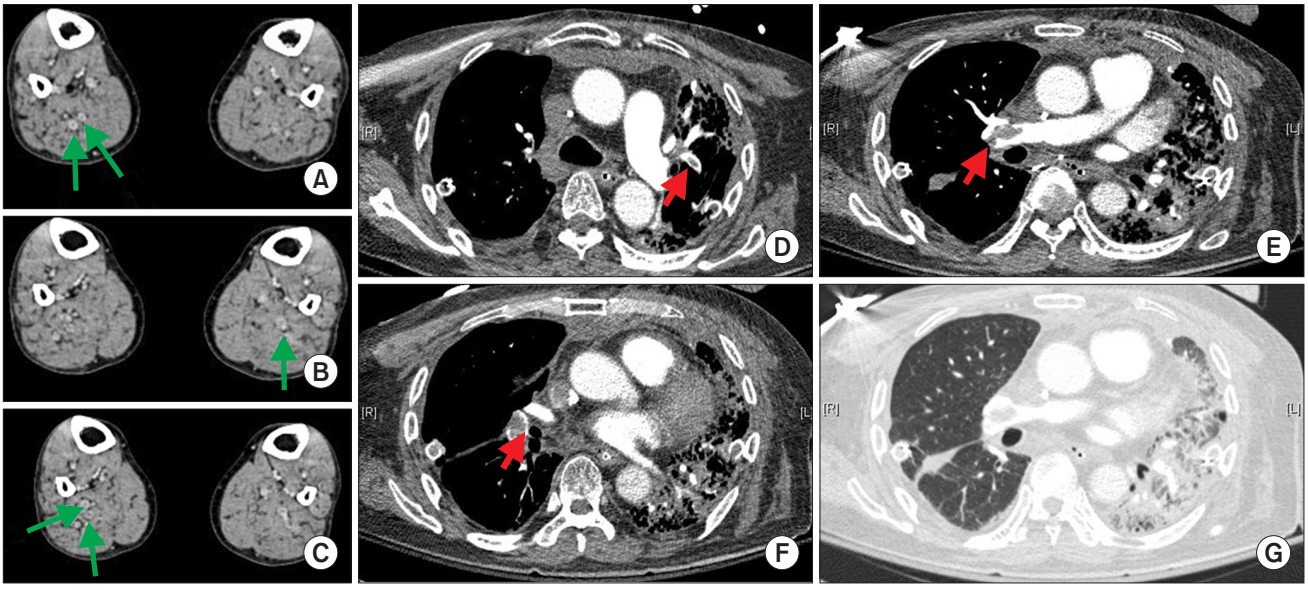


Fig. 10. (A–G) A 58-year-old male patient who underwent lung transplantation due to idiopathic pulmonary fibrosis. At 10 days post-lung transplantation, a chest spiral computed tomography (CT) scan and leg extremity CT scan showed deep vein thrombosis and pulmonary thromboembolism (arrows).

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events [108]. The relationship of these neurologic complications with mortality after LT remains unknown. For the diagnosis of stroke, LTRs are initially evaluated for changes in mental status and neurobehavior. In patients with suspected stroke, a prompt brain magnetic resonance imaging (MRI) evaluation is crucial.

Encephalopathy

Alterations of consciousness and encephalopathy are common after LT presenting as mental confusion, delirium, stupor, and even coma. The risk factors of encephalopathy are severe hyperammonemia, neurotoxicity by immunosuppressive agents, hypoxic-ischemic injury, and graft dysfunction. Severe hyperammonemia in LTRs after the early post-LT period is rare, but can cause mental status changes, cerebral edema, and even death [49,50]. The majority of complications associated with the adverse effects of CNIs are tremor, headache, and paresthesia.

PRES, which manifests with altered consciousness, seizures, or cortical blindness, is a rare neurologic complication associated with CNIs in the early postoperative period after LT (Fig. 11). PRES occurs in approximately 0.5%–5% of patients after SOT [111]. PRES occurs in various clinical conditions, such as hypertension, eclampsia, renal disease, immunosuppression, and severe infection or sepsis [112]. Brain MRI shows multiple cortical and subcortical hyperintense foci in the occipito-parietal lobes associated with vasogenic edema (Fig. 11) [112]. Temporary cessation of CNIs and administration of alternative immunosuppressive agents such as basiliximab may be effective strategies for the management of PRES. In addition, strict BP control and management of seizures is required. The prognosis of PRES is usually good and it rarely relapses if its risk factors are appropriately managed [111].

Seizures

The prevalence of seizures is estimated to be 23% in the post-LT period [113]. Neurotoxicity caused by immunosuppressive agents, cerebrovascular diseases and infections, and severe hyperammonemia is related to the development of seizures after LT [108,113]. The management of seizures in LTRs is similar to that in the general population.

Osteoporosis and musculoskeletal complications

Osteoporosis is a significant complication that can potentially affect morbidity and mortality in LTRs. The continuous loss of bone density contributes to an increased risk of fractures and decreases the quality of life after LT [114]. Reduced bone mass in patients with advanced lung disease who are candidates for LT is related to osteoporosis and fractures [114,115]. Osteoporosis occurs in approximately 30%–50% of these LT candidates [115,116]. Postmenopausal status, diabetes mellitus, malnutrition, vitamin D deficiency, lower sex hormone levels, and preexisting bone mineral abnormalities are risk factors for osteoporosis. Of these factors, immunosuppressive therapy and preexisting osteopenia are closely related to the development of osteoporosis after LT [117].

The post–LT fracture rate is 6%–18% within the first year after LT, and the bone mineral density loss is 4%–12%.

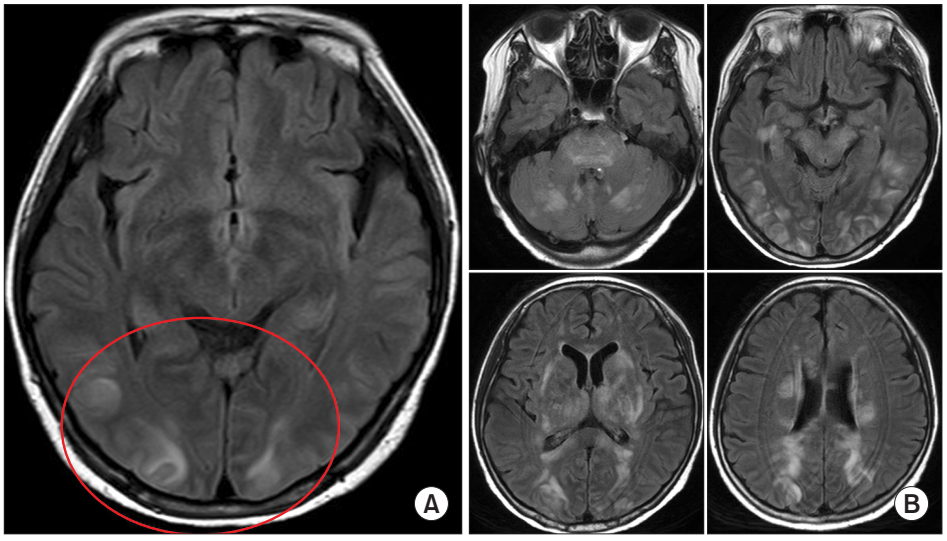

Fig. 11. A 59-year-old female patient who underwent lung transplantation due to destroyed lung and cor pulmonale. (A) At 1 month post-transplant, posterior reversible encephalopathy syndrome (PRES) first developed with seizures, hallucinations, and drowsiness (red circle). (B) After 3 months, PRES relapsed with seizures and high blood pressure.

The guidelines for SOT recommend a bone density evaluation using dual-energy X-ray absorptiometry for all transplant candidates and starting bisphosphonate treatment in patients with moderate to severe osteopenia and osteoporosis for at least 6–12 months after transplantation [117], or long-term life-long therapy [118].

Increased physical activity and supplementation of calcium and vitamin D are required [117]. In addition, if glucocorticoids induce further bone changes during the 6-month period after the transplant, a dose reduction is necessary. According to the Fracture Risk Assessment Tool score, medical treatment including bisphosphonates begins after the diagnosis of osteoporosis [119,120].

Psychiatric complications

Mood disorders and post-traumatic stress disorder

Mood and anxiety disorders are common psychiatric conditions after LT. Depression or anxiety disorders occur in about 30% of patients in the first year post-LT and persist in many LTRs [121]. The most important risk factor for mood disorders is the pre-transplant presence of anxiety or depression. In patients with advanced lung disease, decreased physical function and social support, longer transplant waiting time, female sex, and early post-transplant complications are closely related to the development of mood disorders [122]. Prior studies have shown that mood disorders after LT increased the rates of other complications and clinical outcomes [121,123].

The development of post-traumatic stress disorder (PTSD) is a significant psychiatric complication after LT. Traumatic experiences in the ICU after LT are related to PTSD among LTRs [121,124]. Younger age, lifetime history of a psychiatric disorder, and the use of ECMO as a bridge to LT are associated with the development of PTSD [125, 126].

Delirium

Post-LT delirium is associated with increased duration of hospilization and use of MV, and it is related to worse neurologic outcomes; however, it is not associated with mortality [109,127]. The risk factors for delirium in LTRs are the use of CPB, immunosuppressive medications, and decreased cerebral perfusion during the operation [109,128]. Supportive care and correction of the underlying causes are the main standard treatments. The current guidelines suggest a psychosocial assessment in the initial LT evaluation [129].

Post-transplant lymphoproliferative disorder

Malignancy is the second most common cause of death 5–10 years after LT, occurring in about 17% of LTRs [8]. High-intensity immunosuppressive therapy is related to the development of cancer [130]. Viral infections or reactivation, skin cancer after exposure to the sun, impairment of antitumor and antiviral T-cell immune surveillance from chronic immunosuppressive therapy, and rarely donor-derived malignancies induce post-LT cancer development [131].

In a South Korean study on incident lung cancer after LT, among 247 LTRs, 6 (2.4%) were diagnosed with incident lung cancer among those who had Interstitial lung disease [132].

The incidence of post-transplant lymphoproliferative disorder (PTLD) in LTRs ranges from 2% to 9%, but may be up to 30% in cases where the donor is seropositive for EBV and the recipient is seronegative [130,133,134]. PTLD is associated with worse long-term outcomes and high mortality [134]. PTLD can develop at any time after LT. Early-onset PTLD is typically seen in LTRs who have not had prior EBV infection, in whom the infection is transmitted from the donor. Late PTLD (after 1 year post-LT) originates from T-cell and natural killer cell activity, not EBV [130]. Nonetheless, most cases of PTLD are associated with EBV infection in LTRs. Current guidelines recommend annual chest CT scans for screening of the lung allograft and cancer development. Regarding PTLD, the EBV viral load should be closely monitored, and ganciclovir prophylaxis is associated with a reduced risk of PTLD [135].

Consideration should be given to the use of immunotherapeutic approaches, such as the infusion of EBV-specific cytotoxic T-lymphocytes for cases refractory to other approaches.

Pulmonary PTLD presents nonspecific and involved organ-specific symptoms and radiologic findings such as multiple pulmonary nodules or masses, while GI PTLD manifests as abdominal pain and hemorrhage. The treatment of PTLD is a careful reduction in immunosuppression to enhance the cell-mediated immune response against EBV-infected cells, anti-B cell therapy with rituximab, chemotherapy, and surgical resection or radiation therapy for localized disease [136-138]. A single center in

South Korea reported 2 cases of PTLD presenting with multiple pulmonary nodules in the transplanted lung; these patients rapidly died [139].

Conclusion

We have discussed the common medical complications in LTRs according to the organ systems involved. Transplant physicians should be accustomed to these medical complications, which significantly affect the short- and long-term outcomes after LT, and do their best to manage them. The care of complicated LTRs should be managed through a multi-disciplinary team-based approach with many different fields of specialists for the best outcomes.

ORCID

Moo Suk Park: https://orcid.org/0000-0003-0820-7615

Author contributions

All work was done by Moo Suk Park.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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