

Uncommon Complications of Lung Transplantation in a Referral Center

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Background: Many efforts were made to determine the uncommon clinical complications after lung transplantation and treatment options to tackle them; however, many of these rare complications have not been mentioned in recent publications. Evaluating and recording adverse effects after organ transplantation can significantly prevent post-transplant mortality. This study aimed to examine rejection factors by examining individuals undergoing lung transplantation surgery.

Materials and Methods: In a prospective longitudinal study, we followed up on complications of 60 lung recipients post lung-transplantation surgery for six years from 2010 to 2018. All complications were recorded in follow-up visits or hospital admissions during these years. Finally, the patients' information was categorized and evaluated by designing a questionnaire.

Results: From a total of 60 transplant recipients, from 2010 to 2018, 58 patients were initially enrolled in our study, but two were lost to follow-up. Uncommon complications witnessed in the post-transplantation period included endogenous endophthalmitis, herpetic keratitis, duodenal strongyloidiasis, intestinal cryptosporidiosis, myocardial infarction, diaphragm dysfunction, Chylothorax, thyroid nodule, and necrotizing pancreatitis.

Conclusion: Meticulous postoperative surveillance is crucial for managing lung transplant patients for early detection and treatment of common and uncommon complications. Therefore, it is necessary to establish procedures for assessing the patients' constancy until complete recovery.

Key words: Lung transplantation; Transplant rejection; Uncommon complications; Endogenous endophthalmitis (EE)

INTRODUCTION

Lung transplantation (LT) has emerged as the only treatment for many end-stage lung diseases (1). The first human lung transplantation was performed in 1963 (2). Between 1963 and 1974, 36 patients underwent lung transplantation at medical centers worldwide (3). Beginning in 1981, heart-lung transplantation (HLT) was performed for pulmonary vascular diseases; single lung transplantation (SLT) for pulmonary fibrosis followed in 1983, and double lung transplantation for obstructive lung

disease in 1986 (4,5). Today, lung transplantation is carried out worldwide, the scope of patients' activity has expanded rapidly, and postoperative outcomes have improved significantly.

Along with LT's advantages, its resultant limitations have also become apparent. LT improves the quality of life (QOL) and survival of the recipients. However, survival and QOL are compromised by post-LT infectious and non-infectious complications (6). Although uncommon post-LT complications have not yet been studied extensively, they

significantly impact the survival and patients' QOL. Uncommon complications also increase the morbidity and mortality of patients; therefore, early diagnosis and management of these complications could decrease mortality and morbidity. In this study, we have followed up and managed uncommon complications of post-LT in 6 years of a follow-up study.

MATERIALS AND METHODS

In a longitudinal prospective study, we surveyed post-LT rare complications in 60 patients who underwent LT between 2010 and 2018 at Masih Daneshvari hospital in Tehran. Unclassified uncommon complications were recorded in these 60 patients during the follow-up time. All patients' data were collected in medical records filed in the hospital transplant department. All patients were regularly visited based on a set protocol during the follow-up time. Information was collected from patients, and the time from LT to the occurrence of complications was recorded in a specific datasheet. After preparing the questionnaire and recording the information, the classified information was evaluated qualitatively.

RESULTS

Sixty patients (17 males and 43 females) who underwent LT between 2010 and 2018 were enrolled and surveyed for the incidence of uncommon post-LT complications. The mean age of patients was 35.5 ± 8.6 . Uncommon complications are listed in table 1.

Based on the results, 10 cases from all lung recipients presented with uncommon conditions during the post-lung transplantation period. Depending on the complication type and severity, symptoms appeared at different times after surgery. All of these individuals received the appropriate treatment (Table 1). However, what turned out to be surprising was the significant incidence of uncommon conditions (16.6%) in postoperative lung transplantation for patients.

DISCUSSION

Organ transplantation is one of the most dangerous treatments in the world (7). This treatment has always accompanied challenges such as patient death, rejection, shock, and post-surgical abnormalities (3).

Table 1. Uncommon infectious and Non-infectious complications of post-lung transplantation

Uncommon complications of post-lung transplantation							
infectious complication				Non-infectious complications			
N	Involvement	Treatment method	Time to start the symptoms (month)	N	Involvement	Treatment method	Time to start the symptoms (month)
1	Endogenous endophthalmitis (EE)	Antibiotic	7	1	Myocardial infarction	PCI	1
1	Herpetic Keratitis	GCV	18	1	Chylothorax	Low fat diet	0.5
1	GCV Resistant CMV	Foscarnet, Sirolimus	6	1	Diaphragm dysfunction	BIPAP	-
1	Duodenal Strongyloidiasis	Albendazole	-	1	Necrotizing Pancreatitis	Conservative	0.5
1	Intestinal Cryptosporidium	Conservative	-	1	Thyroid Nodule	Surgical lobectomy	12
					Ascites secondary to Tacrolimus	Switch Tacrolimus to Cyclosporine	-
					Myocarditis to Itraconazole	discontinue Itraconazole	

GCV: Ganciclovir

Hence, various teams of researchers and therapists worldwide work to reduce the risk of organ transplants and prevent them. Understanding the risks of these surgeries and studying each can help anticipate and eliminate probable complications. Lung transplantation, as one of the most challenging types of organ transplantation, is no exception. Patients undergoing this organ transplantation often present uncommon infectious and non-infectious postoperative complications (8). In this study, we studied uncommon post-lung-transplant complications, which warrant greater vigilance from attending physicians during follow-up visits. Many of these complications are secondary to uncommon infectious agents.

Ophthalmic complications are rare in post-lung-transplant patients. Endogenous endophthalmitis (EE) was observed in 1 patient, and herpetic keratitis was observed in another patient. In total, ocular complications were observed in 3.5% of our patients. In a study on 545 patients who received a lung transplant, the most common ocular finding was posterior subcapsular cataract, found in 28.3% of patients (9). In another study, infectious ocular complications were present in 13% of patients (10). Based on previous reports, ocular complications occurred in 2% of patients undergoing heart-lung transplantation, with 65% of these being opportunistic infections. Herpes retinitis (77%) and fungal chorioretinitis were observed in 22% of patients (11), whereas later reports showed lower incidences of ocular infective complications (12). EE is frequently associated with many underlying systemic risk factors, including diabetes mellitus and immune suppression (malignancy, HIV, immunosuppressive therapy) (13,14). Therefore, EE should be highly suspected in postoperative lung recipients with decreased visual acuity.

Herpetic keratitis is the most common ocular complication of HSV. Without prophylactic anti-HSV therapy, HSV seropositive patients are at risk for reactivation of HSV after lung transplantation, even without a history of a full-blown systemic HSV infection.

Herpetic keratitis has several risk factors, including immunosuppressive therapy and decreased immune system function (15,16).

Ganciclovir-resistant Cytomegalovirus (CMV) infection occurred in one of our patients during follow-up. CMV is the most common opportunistic infection in lung transplantation. Resistance to GCV could be secondary to immune suppression in post-transplant patients. Our patient was a case of pulmonary microlithiasis that underwent one-sided lung transplantation. Six months after the transplantation, CMV viral load increased to 18500 IU/ml, and even after GCV therapy, the viral titer increased to 22900 IU/ml. Foscarnet replaced GCV and cyclosporine was switched to sirolimus. Since then, the serology test became negative for CMV and remained so during the follow-ups. A similar study showed that the incidence of CMV infections decreased in sirolimus compared to azathioprine after lung transplantation. Cytomegalovirus (CMV) infections have become less frequent due to prophylactic doses of GCV. Resistant CMV is rarely seen in post-lung transplant patients. The overall incidence of CMV infection was decreased in sirolimus patients compared to azathioprine cases one year after lung transplantation (17).

Myocardial infarction was diagnosed in one of our patients, and it has been reported previously (18). Although it is a rare complication in lung transplantation, cardiac transplant vasculopathy (CTV) is a significant complication and a leading cause of death in heart transplant patients (19). Pathogenesis of acute myocardial infarction after lung transplantation surgery is not yet well understood, but it could be related to age, CAD risk factors, and other comorbidities (20). All transplanted patients have an elevated risk of myocardial infarction. Thrombosis can also be the consequence of the surgery or immune-related inflammation. On the other hand, immunosuppressive therapy may lead to metabolic and hemostasis imbalance that increases the risk of thrombosis and myocardial infarction. In post-lung-transplant operation, patients with symptoms of MI should be

worked up for the possible emergence of gas emboli originating from the anastomosis site (21). Our patient was a case of chronic obstructive pulmonary disease (COPD) with extensive anterior MI. Angiography revealed sclerosis in the Left main coronary treated with PCI.

Acute pancreatitis is not a rare complication in transplant recipients. In a study, the incidence of acute pancreatitis in liver transplant recipients is reported as high as 3-5.7% suffering from a high mortality of 64%. Risk factors in liver transplant recipients include interferon, hepatitis B, alcohol, pancreatic malignancy, hepatobiliary manipulations, CMV infection, alcohol, cholecystitis, and immune suppression (22). However, the incidence of these complications in patients undergoing lung transplantation is not unexpected.

Myocarditis associated with itraconazole was found in one patient in this study. Other studies have confirmed the congestive heart failure associated with itraconazole (23). Animal and clinical pharmacology studies suggest negative inotropic effects of itraconazole. Adverse cardiovascular events associated with itraconazole were not uncommon (24). Our patient suffered from dyspnea and a decreased ejection fraction (EF) in serial echocardiography. After discontinuation of itraconazole, EF improved to 50% after ten days, and the patients' general condition was healed. Therefore, it is recommended that lung transplant recipients who receive itraconazole be monitored for myocarditis, and any sign of CHF should be considered gravely, followed by discontinuing itraconazole.

Thyroid Nodule was detected in one of the patients, who was a case of Pulmonary Langerhans cell histiocytosis (PLCH), after bilateral lung transplantation. Ultrasound depicted a hyperechoic nodule, and further FNA workup revealed a benign follicular nodule one year after LT. Total thyroidectomy and frozen section analysis demonstrated papillary cell thyroid carcinoma (PTC). Pathology studies reported Langerhans cells infiltration in interstitial thyroid tissues. Immune suppressive therapy increases the risk of the progression of malignancies in transplant recipients.

In a study on 1739 kidney transplant recipients, 7.4% grew malignancy, from which 0.7% was PTC. Most cases had optimal outcomes; therefore, frequent thyroid ultrasound screening is recommended to ensure a good prognosis and treatment (25).

Chylothorax is a potentially serious but rare complication of lung and heart-lung transplantation (26). Chylothorax occurred in one of the cases. Damage to the thoracic duct could explain chylothorax. In a study, they described the clinical course of chylothorax in 3 heart-lung allograft recipients. After shunt placement, patients had complete resolution of the chylous effusion without subsequent side effects (27). Another report described a case of a bilateral chylothorax that occurred in a 53-year-old man four months after heart-lung transplantation (28). Our patient had chylothorax 17 days after the transplant and was diagnosed with massive pleural effusion and triglyceride 228 mg/dL in paracentesis. The condition was improved spontaneously by using a low-fat diet after several weeks.

In another patient who underwent left lung transplantation, unilateral left diaphragmatic paralysis developed after the surgery, marked by left hemidiaphragm elevation in a CT scan. Based on previous studies, diaphragmatic paralysis is a rare complication of lung transplantation. Dissection of the mediastinum and manipulation of the pericardium is performed during lung transplantation; therefore, phrenic nerve injury could occur as a complication of the surgery, yet postoperative diaphragmatic paralysis has rarely been reported (29,30). Mogayzel et al. reported bilateral diaphragm paralysis following bilateral lung transplantation and cardiac surgery in a 17-year-old patient (29). Maziak et al. reported a review of 185 single and sequential single lung transplant procedures, which showed unilateral diaphragm paralysis in 5 patients (all were left-sided) and bilateral in 1 patient associated with longer intensive care unit stay and hospitalization (30). In our patient, left-sided diaphragm paralysis increased ICU admissions and continuous BiPAP ventilation, which induced optimal VBG in follow-ups.

Another case had strongyloidiasis hyper infection 11 months after the transplant. This case presented with abdominal pain and diarrhea, in which the larva was detected in a stool exam and confirmed by duodenal biopsy. Albendazole 400 mg/Bid was administered, and the patient was treated after ten days. *Strongyloides stercoralis* is an intestinal nematode that causes intestinal infections that may be asymptomatic for years. It can occur during immunosuppressive or corticosteroid therapy autoinfection, resulting in hyperinfection syndrome. In a patient report, Galiano et al. showed *Strongyloides stercoralis* hyperinfection syndrome two months after simultaneous kidney/pancreas transplantation (31). Another patient had intestinal *Cryptosporidium* 11 months after surgery. Its manifestations were diarrhea, tenesmus, and abdominal pain demonstrated by cysts detected in stool exams. Immunosuppressive therapy was diminished, and conservative therapy continued until abdominal pain waived over time. *Cryptosporidium Parvum* is an intracellular parasite that induces gastroenteritis (GE). In immune-competent patients, GE is self-limited, but in immune-compromised patients, it manifests as a persistent life-threatening disease. Few reports are available of this opportunistic infection in solid organ recipients. Diarrhea is a non-specific symptom in these patients that could be induced by immune-suppressive therapy or opportunistic infections. Cryptosporidiosis should be recognized as an important cause of diarrhea after solid organ transplant and is associated with tacrolimus (32). Another report is about a patient who had cryptosporidiosis after a kidney transplant and presented with diarrhea and negative smear and culture as well as PCR test but positive *Cryptosporidium* oocysts in stool by modified Kinyoun staining (33). *Giardia* and *cryptosporidium* are the most common intestinal parasites in solid organ transplant recipients, particularly in endemic regions. Their prevalence is even more common in developing countries, reported as up to 20% (34).

CONCLUSION

Due to the susceptibility of patients to organ transplant surgery, any contamination caused by infectious or non-infectious agents can cause irreparable damage to the patient. The use of various types of drugs, the general weakness of the body as a result of surgical stress, and suppression of the immune system are all factors of this vulnerability. In this way, the care of these types of patients (to normalize the patient's physical condition) should be put on the agenda of the treatment team. Therefore, meticulous follow-up and surveillance in the post-lung transplant period are crucial for managing these patients for early detection and treatment of common and uncommon complications. Thus, establishing a monitoring unit on patients' conditions after organ transplantation is essential in ensuring the patient's recovery process.

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