Early View

Review

Recurrence of primary disease following lung transplantation

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RECURRERNE OF PRIMARY DISEASE FOLLOWING LUNG TRANSPLANTATION

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ABSTRACT

Lung transplant has become definitive treatment for patients with several end-stage lung diseases. Since the first attempted lung transplantation in 1963, survival has significantly improved due to advancement in immunosuppression, organ procurement, ex-vivo lung perfusion, surgical techniques, prevention of chronic lung allograft dysfunction, and bridging to transplant using extra-corporeal membrane oxygenation. Despite a steady increase in number of lung transplantations each year, there is still a huge gap between demand and supply of organs available, and work continues to select recipients with potential for best outcomes. According to review of the literature, there are some rare primary diseases that may recur following transplantation. As the number of lung transplants increase, we continue to identify disease processes at highest risk for recurrence, thus shaping our future approaches. While the aim of lung transplantation is improving survival and quality of life, choosing the best recipients is crucial due to shortage of donated organs. Here we discuss the common disease processes that recur and highlight its impact on overall outcome following lung transplantation.

INTRODUCTION

Over the past 40 years, lung transplantation (LTx) has become a definitive treatment for patients with a variety of end-stage lung diseases. According to the International Society for Heart and Lung Transplantation (ISHLT), more than 100,000 LTx have been performed over the years. The 2018 registry report showed the median survival for all adult LTx recipients to be 6.5 years [1]. Lung transplantation should be considered for adults with advanced lung disease who meet the following criteria: (I) High (>50%) risk of death due to lung disease within 2 years if the transplantation is not performed; (II) High (>80%) likelihood of surviving at least 90 days after lung transplantation; (III) High (>80%) likelihood of 5-year post-transplant survival provided there is adequate graft function [2].

Disease based indications include idiopathic pulmonary fibrosis (IPF), fibrosing nonspecific interstitial pneumonia (NSIP) and other progressive interstitial lung diseases (ILD) refractory to treatment, ILD related to collagen vascular diseases (scleroderma, rheumatoid arthritis), chronic obstructive lung disease (COPD), bronchiectasis (cystic fibrosis or non cystic fibrosis),
pulmonary hypertension, alpha-1 antitrypsin deficiency, sarcoidosis, obliterative bronchiolitis, lymphangioleiomyomatosis (LAM), pulmonary Langerhans' cell histiocytosis (PLCH) and retransplantations [3].

Incidentally, number of conditions can recur following LTx and may involve the transplanted organs. Here, we review conditions leading to transplant with potential for recurrence and the impact of such recurrences on the overall outcome following LTx.

LYMPHANGIOLEIOMYOMATOSIS

Lymphangioleiomyomatosis (LAM) is a rare, female-predominant, low-grade neoplastic disorder with a prevalence of two per one million [4]. It is a progressive, cystic lung disease with abnormal proliferation of atypical smooth muscle-like cells and is either sporadic (S-LAM) or related with tuberous sclerosis complex (TSC-LAM) [5]. The disease course of LAM is variable and ranges from mild, stable disease to progressive respiratory failure, with an estimated median survival of over 20 years [6].

Histologically, the LAM cells have both melanoma related antigens and smooth muscle antigens which are useful for identification [4]. LAM cells possess bi-allelic inactivation of TSC, a tumor suppressor gene that activates mTOR pathway which leads to an uncontrolled proliferation and metastasis of LAM cells.

The goal of treatment aims mainly the relief of symptoms and management of complications. MILES study showed that sirolimus treatment could stabilize the function of lung and improve the quality of life [7]. On the other hand, Oprescu et al. [8] in 2013 showed that such therapy doesn’t improve the outcome of disease.

In patients with respiratory failure who have exhausted all medical therapies, LTx may be the only recourse [9]. The first reported lung transplant procedure for LAM was a combined heart-lung transplantation in 1984 [10]. According to 2019 ISHLT data, a total of 582 LTx were performed for LAM between years 1995 and 2018 [11, 12].

The recurrence of LAM (R-LAM) following LTx is rare and only 23 cases have been reported in the literature. It is evident that LAM could recur as early as within two months after LTx (Figure 1, 2). The database from Europe and Japan demonstrated a recurrence rate around 6%-7% for
LAM after transplantation [13-15]. The recurrence is rare, and the post-transplant survival of these patients when compared to other indications is better and does not compromise long term survival. The estimated five-year post-transplant survival among LAM patients is between 60%-70% [13-14,16].

Regarding the possible mechanism of recurrence, genetic analysis by Karbowniczek et al. concluded that LAM cells metastasize to the allograft lung after transplantation, despite their histologically benign features. This is likely facilitated by immunosuppression along with genetic predisposition [5].

It is not very clear when to start mTOR inhibitors as LAM recurrence is mostly asymptomatic. It is unlikely that a large, randomized trial among these patients is feasible due its rarity; however, we suggest that in LTx recipients with LAM, sirolimus should be considered as a primary anti-rejection medication either as a mono or as a dual therapy with a calcineurin inhibitors (CNI) [17]. This can be done in the context of CNI-sparing regimens or using a second antiproliferative medication instead of Mycophenolate or Azathioprine. Whether these would benefit from life-long mTOR-inhibitor therapy remains to be established.

Patients undergoing LTx for LAM have acceptable morbidity and satisfactory survival. The median survival following LTx in LAM is 12 years and better than other lung diseases [18]. It is important to investigate the possibility of disease recurrence post-transplantation in patients who have deteriorating lung function. Intolerance or complications of mTOR inhibitors may limit their use in some patients, who may then require retransplantation. In the literature, only 5 LAM patients underwent retransplantation [19-21]. Two of them were due to graft failure [20] and bronchiolitis obliterans syndrome [21]. To date, there are no reported cases of LAM patients receiving a transplant for recurrence in the allograft. It is unclear at this stage if mTOR inhibitors or any hormonal therapy can delay or prevent recurrence in the allograft [22-32].

**SARCOIDOSIS**

Sarcoidosis is a multisystem disease of unknown etiology that predominantly affects the lungs and lymph nodes. The histological hallmark of sarcoidosis is the formation of noncaseating epithelioid cell granulomas in affected organs. The T-cell function plays a role in the development of the disease [33, 34]. The prognosis of patients with isolated pulmonary
sarcoidosis is generally good. A majority of these patients undergo spontaneous remission within 2 to 5 years. Patients with stage I (according to radiological Scadding stage) disease have over 80% rate of resolution compared with stage II (60%) or stage III (30%) disease. A small number of patients may progress to end-stage lung disease. Mortality ranges from 1 to 6%, with the majority of deaths resulting from respiratory failure [35]. Despite treatment, some individuals develop end-stage lung disease due to parenchymal fibrosis. In stage 3 and 4 patients, disease progression may lead to irreversible destruction and chronic respiratory failure. According to 2019 ISHLT data, a total of 1540 (2.4%) LTx were performed for sarcoidosis between 1995-2018 [11]. Indications for LTx in sarcoidosis are functional capacity III and IV, pulmonary hypertension, right atrial pressure of over 15mmHg and hypoxemia at rest [12]. Five-year survival following LTx for Sarcoidosis is between 47% and 69% [36-38].

Sarcoidosis is the most commonly reported disease to recur post-LTx with an estimated rate of 47%. [39]. A recent article reported the recurrence to be 14% thus suggesting that the rate could be influenced by the immunosuppressive regimen which has changed in years [38]. Ionescu et al. showed via DNA analysis that recurrence of granulomas in the allografts appear to be of recipient origin [40]. The granulomas appear within the first 6-12 months post-transplant, are usually detected via surveillance biopsies, and rarely seem to have a significant impact on allograft function. [41-42]. A case has been reported of sarcoid recurrence after single lung transplantation (SLT), necessitating repeat transplantation, which was followed again by sarcoid recurrence. This report favors bilateral lung transplantation (BLT), which provides a greater functional reserve in case of disease recurrence compared to SLT, and also prevents infections from persistent bronchiectasis [38,43]. The first case series related to recurrent sarcoidosis was published by Johnson et al. in 1993 [44]. The onset of sarcoidosis was seen as early as 2 weeks after the transplantation, mostly within first 3 months and as late as 2 years [40,44-46]. The disease tends to be milder in its clinical manifestations than primary disease, possibly due to anti-rejection regimen. Recurrent sarcoidosis may also manifest clinically as either a solitary or numerous miliary nodules [43, 47-48]. Because the granulomas can be focal and patchy, a negative biopsy does not exclude recurrent sarcoidosis. Normal organs transplanted into recipients with pre-existing sarcoidosis are likely to develop sarcoid granulomas, whereas organs from donors with known sarcoidosis transplanted in a non-sarcoid recipient do not appear to
develop significant or progressive disease. “Donor-acquired sarcoidosis” is development of sarcoidosis in presumably naive recipients who have received tissues or organs from donors who were not known or suspected to have active sarcoidosis. [40].

The etiology of sarcoidosis is not known with certainty despite decades-long effort. It is generally thought that it is the result of an exaggerated immune response in a genetically susceptible individual to an undefined antigen, such as certain environmental factors, microbes (e.g., *Mycobacterium tuberculosis, Propionibacterium acnes*), or partially degraded antigens. Currently, it is believed that both genetic predisposition and environmental factors play essential roles in its pathogenesis [44]. Additionally, in a subclass of patients, an increased usage of the γδ-T cell receptor has been found, which is a similar phenomenon seen in patients with tuberculosis. Mycobacterial DNA was demonstrated in lung cells obtained from patients with sarcoidosis using polymerase chain reaction. The interesting observation of recurring sarcoidosis in patients undergoing LTx may reflect the infectious nature of this disorder, since transmission was observed from donor to recipient as well as from recipient to the donated organ [44, 49-50].

The decreased occurrence of sarcoidosis relapses from 2013 onwards suggests a role for mTOR inhibitors, which became more widely used to prevent rejection and might inhibit granuloma formation [38, 51-52]. In addition, there is a possibility that the switch from cyclosporin to tacrolimus in the early 2010s might be implicated in the decreased incidence of relapses yet, the hypothesis remains to be proven [38].

Although recurrence of granulomas in transplanted lungs may occur, this rarely has a significant impact on lung allograft function or recipient survival [41, 53]. The presence of active granulomas on the explanted lung may be a useful predictor of subsequent recurrence. However, recurrence has neither been shown to significantly affect graft function nor worsen the outcomes of these patients. It can easily be treated with systemic corticosteroids. When referring such patients for retransplantation, careful consideration of the benefits and risks of lung transplantation must be made. In a rare and unlikely case of respiratory failure due to recurrent sarcoidosis of the transplanted lung, retransplantation should be assessed on an individual basis and adjustment of the immunosuppressive regimen should be taken into account. Furthermore, extrapulmonary sarcoidosis involvement should be excluded.
PULMONARY LANGERHANS CELL HISTIOCYTOSIS

Pulmonary Langerhans cell histiocytosis (PLCH) is a rare, smoking-related cystic lung disease that can progress to respiratory failure and severe pulmonary hypertension. It is caused by a disorder of myeloid dendritic cells. No occupational or geographic predisposition has been reported, but nearly all affected individuals have a history of current or prior cigarette smoking [60-61]. PLCH is estimated to account for 3-5% of adult diffuse parenchymal lung diseases. Langerhans cells are normally found in low numbers in the dermis, the reticuloendothelial system, the lung, and the pleura. In PLCH, the Langerhans-like cells, which express CD1a, S100 protein, and langerin (CD207), are characteristically found in clusters. Somatic mutations that activate the mitogen-activated protein kinase (MAPK) pathway are present in virtually all cases of Langerhans cell histiocytosis (LCH) and PLCH. In both LCH and PLCH, the most common variants are BRAF V600E and MAPK2K1 genes encoding protein kinases, but numerous others have been described [62]. Smoking promotes accumulation of non-neoplastic CD1a dendritic cells around airways and may also promote maintenance of CD1a cells with oncogenic mutations [62].

Extrapulmonary LCH is noted in less than 20 percent of reported cases of PLCH [63]. When present, bone lesions, diabetes insipidus, and skin lesions can be seen. PLCH should be suspected in all patients with upper lung zone cystic or nodular radiographic abnormalities, or a history of recurrent pneumothorax, diabetes insipidus, or bone pain. A current or past history of smoking or exposure is an important feature. There are no routine laboratory tests that are diagnostic of PLCH [64]. The finding of more than 5% CD-1a and CD207 positive cells on BAL strongly supports the diagnosis of PLCH [65-66].

For patients without symptoms or pulmonary impairment, smoking cessation and observation without specific therapy is adequate. The optimal therapy for progressive PLCH has not been determined. Systemic glucocorticoids have a limited role. For patients who are not candidates for or do not respond to glucocorticoids, trial of cladribine or cytarabine is suggested with appropriate monitoring of peripheral blood for cytopenia and prophylaxis against opportunistic infections [67]. Lung transplantation is an option for patients with advanced and progressive
PLCH. Precise data regarding prevalence is not available, although a large series of hundreds of patients undergoing surgical lung biopsies for diffuse lung disease reported PLCH in 4-5% of all biopsies [68]. It is an infrequent indication of LTx worldwide, accounting for only 0.4% of adult primary LTx from January 2004 to June 2015 [12]. The recurrence of PLCH after successful lung transplantation is uncommon, with 15 cases in literature [69-74]. Most of the cases of recurrent disease have been described within 5 to 60 months after transplantation. The first case was published by Gabby et al., a 32-year-old non-smoker male who underwent bilateral LTx and had recurrence of disease after 2 years [69]. Etienne et al. reported two cases of recurrence; both had single LTx. These patients resumed smoking early after transplantation [71]. The recurrence of the disease suggests either that extrapulmonary factors play a role in pathogenesis or the disease may be truly neoplastic. The recent demonstration that Langerhans cells in PLCH may proliferate locally, usually showing an abnormal phenotype, lends some support to the latter theory. Why the disease should recur in exactly the same pulmonary distribution before and after transplantation in some patients is unclear [70].

Dauriat et al. published a multi-center analysis of 39 patients with PLCH who underwent LTx. Extra-pulmonary involvement was present in 31%. The survival rate was 76.9% at 1 year, 63.6% at 2 years, 57.2% at 5 years, and 53.7% at 10 years. The recurrence rate was 20% in this patient population with no impact on survival [72]. Three of the patients resumed smoking after LTx. The recurrence rate was significantly higher with extra-pulmonary involvement [72]. Furthermore, smoking cessation and corticosteroids are the treatment options for the recurrence. Response to pulse steroid therapy is usually satisfactory, and symptomatic relief can be achieved together with resolution of infiltrates [73].

Unless symptomatic relief is achieved with medical treatment, retransplantation can be considered. Dauriat et al. performed retransplantation on 3 of 39 patients with PLCH. However, these patients underwent retransplantation for bronchiolitis obliterans syndrome and not for recurrence [72]. In the literature, there are no cases of retransplantation for recurrent PLCH. Nonetheless, the probability of recurrence of the primary disease should be kept in mind, even in patients undergoing retransplantation.

HARD METAL EXPOSURE
Hard metal lung disease (HMLD) is a rare condition that occurs after chronic occupational exposure to cobalt and tungsten carbide. Giant cell interstitial pneumonia (GIP) is distinct and considered pathognomonic for HMLD, although some cases with no apparent hard metal exposure have been reported. It is different from other occupational lung diseases as it does not depend on the cumulative dosage of the agent [73-74]. The giant cells seen on the biopsy (Figure 3) are referred to as cannibalistic cells that engulf neutrophils and lymphocytes, an uncommon biological process called emperipolesis [75].

Treatment consists of cessation of exposure which may facilitate recovery in some patients. However, this is not the option for fibrotic lung disease in which the findings are irreversible. Corticosteroids and other immunosuppressive drugs have been used in some cases but the efficacy is not yet proven [76-77]. Although LTx is a choice for end stage and progressive disease, 2 cases have been reported with recurrence of the primary disease after transplantation even though the exposure to hard metal was not present [78-79]. Frost et al. reported a case with single LTx who deteriorated after 2 years. The autopsy showed no evidence of inorganic particles in the allograft but changes typical for GIP were present [79]. Tarabichi et al. reported a case of single LTx for HMLD complicated by recurrent episodes of lung injury and multinucleated cells involving the allograft [78]. There is lack of data concerning the recurrence of HMLD, but according to these case reports an autoimmune mechanism might be responsible for the recurrence as there was no exposure to hard metal in the post transplant period.

EMPHYSEMA DUE TO ALPHA-1 ANTIMTRYPSIN DEFICIENCY

Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder with 3.4 million people thought to have this disease worldwide [80]. AAT is secreted mainly by the liver and is a key in keeping balance between proteases and antiproteases. It does this by inhibiting the pancreatic trypsin, neutrophil elastase, cathepsin G and proteinase-3 [81]. The organs mainly affected by this are the liver and lungs. The condition leads to early onset emphysema with an incidence rate of 1.9 % [82-83]. Smoking is the main trigger related to the development of lung disease especially for the ZZ phenotype.
Management consists of standard treatment for COPD and augmentation therapy with purified pooled human plasma α1 antitrypsin infusion [84]. For patients whose lung function declines despite optimal therapy, LTx can be an option [85].

According to 2019 ISHLT registry data, the total number of LTx for AATD from January 1995 to June 2018 were 2969 (4.7%) of which 2155 were bilateral [11]. The frequency for retransplantation in AATD patients was 11.8% according to Wallinder A et al., but the reason for this is not well clarified [19]. There are only two case reports that have shown a recurrence of emphysema after the LTx and the common reason was the resumption of smoking [86-87]. Glanville et al. described emphysema on allografts of 2 AATD patients at postmortem examination and smoking is the main cause for the recurrence [88]. On the other hand, as this is a genetic disease, even after LTx the patients may be still at risk for emphysema, but there is not sufficient data if augmentation therapy could be of benefit after transplantation. Thus, a special attention and rehabilitation for this group is required in order to prevent smoking after transplantation. These observations form the basis for continued replacement therapy post-transplantation.

**PULMONARY ALVEOLAR PROTEINOSIS:**

Pulmonary alveolar proteinosis (PAP) is a rare disease which involves accumulation of lipoproteinaceous material in the alveolar space because of insufficient clearance of surfactants by the alveolar macrophages [89]. PAP is classified as genetic, secondary or autoimmune, the latter being the most common [89]. Antibodies against GM-CSF is the main reason for the autoimmune type which further leads to insufficient macrophage clearance of surfactants [90].

The clinical presentation varies from being asymptomatic to dyspnea, cough, weight loss, chest pain, fatigue, fever, and hemoptysis [91-92]. Periodic acid-Schiff (PAS) positive eosinophilic granules are present in the foamy macrophages [89].

The main treatment approach is whole lung lavage which is beneficial in most cases, but a proportion of patients progress to lung fibrosis. Additional therapies like supplemental granulocyte-macrophage colony-stimulating factor (GM-CSF), rituximab or plasmapheresis have been tried in refractory cases. Lung transplantation is a choice for end-stage disease [93]. There are only 3 case reports that describe the recurrence of PAP after LTx [94-96].
The first report was by Parker et al. in 1997 that describes a patient with diagnosis of PAP at 27 but had a bilateral LTx at age of 41. She had a relapse of the disease 3 years after lung transplantation [94]. The other two reports include patients with genetic defects who had a recurrence of disease 26 and 16 months after LTx respectively [95-96]. The underlying genetic defect resulting in persistent pathologic macrophages can enable recurrence of the disease by migration of precursor cells from the bone marrow suggesting that LTx should be performed with caution, and bone marrow transplantation might help in this group of patients.

Interestingly PAP can occur in lung allografts of patients with a different primary disease as well. There are case reports of PAP occurrence after LTx performed for IPF, Eisenmerger’s syndrome and pulmonary hypertension [97-99]. One case with acute myeloid leukemia appearing 5 years after the LTx developed PAP after receiving chemotherapy and had a bacterial pneumonia leading to death [100]. These patients were negative for GM-CSF antibodies. Thus secondary PAP due to alveolar injury from either ischemia, infection, or immunosuppression might have played a role in macrophage dysfunction. On the other hand the mechanisms thought to be responsible for PAP development in lung allografts are present in many LTx patients, but only a few of them progress to PAP. Thus further knowledge is needed if there are any other existing additional risk factors.

**INTERSTITIAL LUNG DISEASES (ILD)**

Diffuse parenchymal lung diseases, often collectively called Interstitial lung diseases (ILD) are a heterogenous group of disorders classified together due to similar clinical, radiographic, physiologic or pathologic manifestations. Idiopathic pulmonary fibrosis (IPF), the most common type of ILD has the poorest prognosis.

According to the ISHLT registry, ILD made up almost 21% of the LTx performed from 1995 to 2018 [11]. Even though there is a tendency for bilateral lung transplantation (BLT), studies have failed to show its superiority over single lung transplantation (SLT) in terms of survival [101-102]. Another issue is the extrapulmonary involvement of ILDs due to connective tissue disorders (CTD) which may complicate LTx procedure.
The most common ILD-associated CTDs are scleroderma (61%), rheumatoid arthritis (13%) and polymyositis/dermatomyositis (12%) [102]. Hypersensitivity pneumonitis (HP) is another type of ILD caused by inhalation of a specific antigen which can be identified in almost 40% of the cases [103]. The main approach of treatment is to avoid the causative agent but in some patients the disease progresses to lung fibrosis inspite of, thus LTx can be a treatment option [104]. Desquamative interstitial pneumonia (DIP) is a rare form of idiopathic interstitial pneumonia (IIP) in which alveoli are filled with pigmented macrophages [105]. Passive or active smoking, occupational exposure, drug reactions and autoimmune diseases have been reported as causative factors [106]. In recent years the term DIP has been replaced with SRIF (Smoking related interstitial fibrosis). Treatment consists of smoking cessation and systemic corticosteroids, yet it can progress to end stage disease, requiring LTx [106].

The most common recurrent disease after LTx among ILDs is DIP. Interestingly, King et al. reported recurrence of DIP as early as 1 month after LTx. Verleden et al. and Kotecha et al. reported cases with disease recurrence after 12 and 14 months respectively [107-109]. Infections like pneumocystis jirovecii, cytomegalovirus and aspergillus pneumonia might have played a role in the recurrence of disease. The recurrence at an early stage resulted in the death of the patient. The other two cases recovered completely [107-109]. Bhatt et al. reported recurrence of NSIP in a 42 year old female patient after BLT [110]. Histology showed accumulation of recipient origin macrophages as early as 2 months post LTx which progressed to interstitial fibrosis, thus emphasizing the importance of host factors for the recurrence of the disorder [110]. Kern et al. reported a single case of HP that recurred 3 years after LTx due to the ongoing exposure to the causative agent [111]. There is also a case report of recurrence of CTD related ILD after LTx. It describes a 15-year old patient diagnosed with polymyositis (PM), unresponsive to immunosuppressive treatment that underwent BLT after bridging with ECMO [112]. The patient had recurrence of primary disease with post-mortem analysis consistent with pulmonary fibrosis with usual interstitial pneumonia (UIP) [112]. Most recently, Scallan et al. described a case of recurrence of non specific interstitial pneumonia of the fibrotic pattern (NSIP-F) in a lung allograft of a patient who underwent BLT for advanced idiopathic fibrotic NSIP (iNSIP-F). It manifested de-novo clinical and serological features of antisynthetase syndrome (anti-SS) 30 months post-transplant, which is the first of its kind ever described. A
possible explanation for the development of anti-SS in the post transplant period is the expression of previously cryptic tissue-specific autoantibodies as a result of the single episode of acute rejection one month post-transplant despite the apparent lack of connective tissue disease in the donor [113-114]. Further studies are needed to establish the risk factors for recurrence in ILD patients after LTx.

**IDIOPATHIC PULMONARY HEMOSIDEROSIS (IPH)**

IPH is a rare condition first described by Virchow in 1864 as `brown lung induration` and is characterized by the clinical triad of hemoptysis, anemia, and pulmonary infiltrates [115]. IPH affects mainly children with 80% of cases in those under 10 years of age [116]. The incidence of IPH is 0.24-1.23 cases per million [117]. The pathogenesis is unknown. Biopsy shows hemosiderin-laden macrophages [118]. Treatment consists of immunosuppressive drugs that include corticosteroids, hydroxychloroquine, azathioprine and cyclophosphamide [118]. LTx can be considered as an option for patients that do not respond to the treatment, develop pulmonary hypertension or have progression to end stage disease. There are two cases reported regarding the recurrence of IPH after LTx [118-119]. Due to rarity of IPH the outcome of LTx in these patients is yet not very clear and the rate of recurrence needs further investigation. Yet according to the present literature, the outcome of disease even if it recurs after LTx is good and responds well to the immunosuppressive drugs.

**BRONCHOALVEOLAR CARCINOMA (BAC)**

Bronchoalveolar carcinoma (BAC) nomenclature has been replaced with adenocarcinoma-in-situ (AIS) and minimally invasive adenocarcinoma (MIA). Both are indications for referral and listing for LTx if the tumor has a diffuse parenchymal involvement causing respiratory failure or a low quality of life together with unresponsiveness to conventional medical therapies [2]. The recurrence of tumor after resection is especially seen in multifocal disease and the survival is usually not more than two years [120]. The poor prognosis and short survival rates have pushed transplantation centers to perform LTx for this group of patients. Perrot et al. reported that patients who underwent LTx for diffuse multifocal BAC and survived after the operation (a total of 22 patients) had a recurrence of primary disease as high as 59 % in a period of 5 to 49 months (a median of 12 months) [120]. Even though the relapse rate was high; the overall disease-free survival for 5 years was around 35% [121]. Another series by Zorn et al. showed a high
recurrence rate of the disease (6 out of 8 patients), but a good survival for the two patients who were disease free and had unrestricted lung function [122]. Another series from Shin et al. reported 3 out of 6 patients who underwent LTx for BAC to have recurrence of disease at 10-, 39- and 48-months post transplant [123]. They showed the recurrence to be of recipient origin by analysing the radiological and pathological features of the tumor [123]. Two other studies also showed that the recurrence of disease has similar features with the primary tumor and the contamination of the allograft with malignant cells from the main airways of the recipient might be the reason. Therefore, better surgical procedures and new techniques are needed to avoid this phenomenon [124-125]. The high recurrence rate for BAC suggests a revision of the criteria for the LTx referral and listing.

**DIFFUSE PANBRONCHIOLITIS (DPB)**

Diffuse panbronchiolitis was first described in Japan in the 1960s. It is a chronic respiratory disease that affects mainly the bronchioles and can progress to obstructive and suppurative diseases that ends up with bronchiectasis [126]. It is characterized by chronic inflammation with mainly lymphocytes, plasma cells, histiocytes, neutrophils, and foamy macrophages accumulating around the bronchioles [127-128]. Macrolides have been shown to be effective in the treatment of DPB, but in patients who do not respond to treatment, or develop pulmonary hypertension and respiratory failure, LTx may be an option [127,129]. There are 2 cases of recurrence of the primary disease following LTx for DPB [128-130].

Chronic sinusitis and colonization with pseudomonas aeruginosa-commonly seen in DPB patients-might be risk factors for the recurrence of the primary disease, thus optimal treatment of these two conditions might help for better outcomes.

**PULMONARY VASCULAR DISEASES**

Patients with pulmonary vascular diseases that are associated with pulmonary hypertension (PH) without a response to targeted medical therapy are also candidates for LTx [2]. Patients with NYHA Functional Class III or IV despite a trial of at least 3 months of combination therapy
including prostanoids, with cardiac index of less than 2 liters/min/m², mean right atrial pressure of more than 15 mm Hg, 6-minute walk test of less than 350 m and development of hemoptysis, pericardial effusion, and signs of progressive right heart failure are the criteria for listing these patients for LTx [2].

Pulmonary capillary hemangiomatosis, idiopathic pulmonary arterial hypertension (IPAH), and pulmonary veno-occlusive diseases are rare causes of pulmonary hypertension that have a poor prognosis and short survival thus LTx remains the only definitive treatment choice. According to 2019 ISHLT data, 2.9% of total LTx were performed for IPAH and 1.5% for other forms of PH [11]. There are only 4 case reports of recurrence following LTx [131-134]. According to these case reports the recurrence of such diseases occur within one year and raises the question if LTx is an appropriate treatment choice for this group of patients. The gaps in our knowledge regarding the pathogenesis of these diseases and the possible extrapulmonary involvement warrants further study.

**CONCLUSION**

According to the analysis of the present literature about the recurrence of primary diseases after LTx, it is obvious that it is a rare entity and rarely associated with worse outcome. There are gaps in our knowledge regarding the pathophysiology, systemic involvement, and risk factors for recurrence on an individual basis and this has potential to influence criteria for lung transplant listings. Risk factors for recurrence should be elucidated and taken into account to further optimize long-term outcome of patients at risk. Furthermore, recurrence of disease should be taken into account in new onset allograft dysfunction, which should be excluded before the diagnosis of CLAD is established. While the aim of LTx is to prolong survival and quality of life for patients with end-stage lung disease, it is crucial to choose the best recipients due to shortage of donated organs.

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Figure 1
Supplementary material

**Table 1.** Recurrence of LAM: Published Literature

**Table 2.** Features of recurrence of sarcoidosis following Lung Transplantation

**Table 3.** The features of recurrence of Pulmonary Langerhans cell histiocytosis following Lung Transplantation

**Table 4.** Recurrence of hard metal lung disease following Lung Transplantation

**Table 5.** Recurrence of Emphysema following Lung Transplantation among patients with Alpha1 Anti-Trypsin Deficiency

**Table 6.** Recurrence of Pulmonary Alveolar Proteinosis following Lung Transplantation

**Table 7.** Recurrence of Interstitial lung disease following Lung Transplantation

**Table 8.** Recurrence of Idiopathic Pulmonary Hemosiderosis following Lung Transplantation

**Table 9.** Recurrence of Bronchoalveolar Carcinoma following Lung Transplantation

**Table 10.** Recurrence of Diffuse Pan Bronchiolitis following Lung Transplantation

**Table 11.** Recurrence of pulmonary vascular diseases following Lung Transplantation
<table>
<thead>
<tr>
<th>Ref</th>
<th>No. of patients</th>
<th>Type of transplant</th>
<th>Age at transplantation (yr)</th>
<th>Donor</th>
<th>Post-transplant immunosuppressive drugs</th>
<th>Post-transplant complications</th>
<th>Outcomes</th>
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<td>Nine JS et al (22)</td>
<td>1</td>
<td>SLT: left</td>
<td>45</td>
<td>Male cadaveric</td>
<td>FK-506 Prednisone Aerolised cyclosporine</td>
<td>Recurrent right PNX Left renal lymphangioleomyoma BOS Pulmonary embolism</td>
<td>COD: disseminated fungal infection R-LAM was confirmed on autopsy (3 years after LT)</td>
</tr>
<tr>
<td>O'Brien et al (23)</td>
<td>1</td>
<td>SLT: right</td>
<td>42</td>
<td>Male cadaveric</td>
<td>Cyclosporine Azathioprine Prednisone</td>
<td>Right chylous pleural effusion AR</td>
<td>COD: post cholecystectomy pneumonia and respiratory failure R-LAM was confirmed on autopsy (2 years after LT)</td>
</tr>
<tr>
<td>Bittmann et al (24)</td>
<td>1</td>
<td>SLT: right</td>
<td>34</td>
<td>Male Cadaveric</td>
<td>NA</td>
<td>AR</td>
<td>1 year after LT OLB: BO 2 years after LT: PNX COD: Aspergillus pneumonia, R-LAM was confirmed on autopsy (2 years after LT)</td>
</tr>
<tr>
<td>Bittmann et al (25)</td>
<td>1</td>
<td>SLT: right</td>
<td>33</td>
<td>Male Cadaveric</td>
<td>NA</td>
<td>NONE</td>
<td>COD: PNX-Right &amp; hypoxemia R-LAM was confirmed on autopsy (2 years after LT)</td>
</tr>
<tr>
<td>Chen et al (26)</td>
<td>1</td>
<td>Living-donor lobar</td>
<td>23</td>
<td>Motheer and sister</td>
<td>NA</td>
<td>Massive chylous PE &amp; ascites</td>
<td>6 months after LT right PE and left PNX R-LAM: left lung 2 years after LT; diagnosed by cysts in CT &amp; TBLB</td>
</tr>
<tr>
<td>Benden et al (13)</td>
<td>4</td>
<td>2 SLT 2 DLT</td>
<td>NA</td>
<td>NA</td>
<td>Cyclosporine or Tacrolimus Prednisone Azathioprine or MMF</td>
<td>NA</td>
<td>2 SLT: both alive &gt;36 months post-transplant, 2 DLT: 1 died 44 months post-transplant due to respiratory failure, and the other was still alive at the end of the study period 110 months post-transplant,</td>
</tr>
<tr>
<td>Authors</td>
<td>Type</td>
<td>Year</td>
<td>Recipient</td>
<td>Donor</td>
<td>Donor Type</td>
<td>Immunosuppression</td>
<td>Cause of Death/LAM Diagnosis</td>
</tr>
<tr>
<td>--------------------</td>
<td>------</td>
<td>------</td>
<td>------------</td>
<td>-------</td>
<td>------------</td>
<td>-------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Zaki et al (17)</td>
<td>BLT</td>
<td>66</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Prednisone, Tacrolimus, Mycophenolate Mofetil</td>
<td>Left upper lobe lobectomy for pseudomonas abscess Aspergillus, Pseudomonas &amp; MAC infection</td>
</tr>
<tr>
<td>Pigula FA et al (27)</td>
<td>SLT</td>
<td>NA</td>
<td>NA</td>
<td>Cyclosporine or Tacrolimus, Azathioprine Prednisone</td>
<td>One pt retransplanted due to PGD &amp; pulm embolism</td>
<td>2 R-LAM identified at autopsy, at 2 months and 30 months after transplantation.</td>
<td></td>
</tr>
<tr>
<td>Sugimoto et al (28)</td>
<td>Bilateral Living-donor lobar</td>
<td>23</td>
<td>Brother</td>
<td>Azathioprine Tacrolimus Prednisone</td>
<td>None</td>
<td>5 years after LT R-LAM occurred based on radiologic findings and deteriorating pulmonary function, her clinical symptoms, which included dyspnea and chylothorax, were significantly improved after treatment with sirolimus.</td>
<td></td>
</tr>
<tr>
<td>Pechet TT et al (29)</td>
<td>SLT</td>
<td>NA</td>
<td>NA</td>
<td>Cyclosporine Azathioprine Prednisone</td>
<td>NA</td>
<td>Diagnosed at autopsy following death from sepsis 22 months after LT</td>
<td></td>
</tr>
<tr>
<td>Reynaud-Gaubert et al (30)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Tacrolimus Prednisone Azathioprine</td>
<td>NA</td>
<td>R-LAM occurred one on the transplanted lung (with specific radiological and histological findings) and the other on mediastinal and retroperitoneal lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Ando et al (15)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Diagnosed by TBLB</td>
</tr>
<tr>
<td>Collins J (31)</td>
<td>SLT</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>R-LAM occurred 24 months after LT, autopsy confirmed</td>
</tr>
<tr>
<td>Taveira-Da Silva et al (32)</td>
<td>BLT</td>
<td>26</td>
<td>NA</td>
<td>Pleural effusions, pneumothocaces, fungal infection</td>
<td>R-LAM occurred 36 months after LT. Multiple cystic lesions in both lungs with elevated VEGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karbowniczek et al (5)</td>
<td>SLT</td>
<td>44</td>
<td>NA</td>
<td>Cyclosporine Azathioprine Prednisone</td>
<td>NA</td>
<td>Diagnosed at autopsy following death from Aspergillus pneumonia 22 months after LT</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Features of recurrence of sarcoidosis following Lung Transplantation

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. of transpl</th>
<th>No of RS</th>
<th>Mean age</th>
<th>Type of tx</th>
<th>Post-transp. IS drugs</th>
<th>DX</th>
<th>Post-transp. complications</th>
<th>Outcomes</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al (44)</td>
<td>5</td>
<td>4 incidental</td>
<td>42</td>
<td>SLT</td>
<td>Cyclosporin Azathioprine</td>
<td>TBLB</td>
<td>AR BO</td>
<td>AR No recurrence after 3 months</td>
<td>NA</td>
</tr>
<tr>
<td>Pigula FA et al (27)</td>
<td>9</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>Cyclosporine or tacrolimus Azathioprine Prednisone</td>
<td>TBLB</td>
<td>1 died due to multiorgan failure</td>
<td>4 IPA</td>
<td>NA</td>
</tr>
<tr>
<td>Walker S et al (37)</td>
<td>12</td>
<td>3, 1 symptomatic</td>
<td>NA</td>
<td>SLT:10 BLT:2</td>
<td>Cyclosporin Azathioprine Prednisolone</td>
<td>TBLB</td>
<td>2 died perop: acute donor organ multifunction; 1 died on 10th day due to the same reason</td>
<td>The granulomas were identified at five, six, and 56 months after tx</td>
<td>5-year survival 56%</td>
</tr>
<tr>
<td>Bjørntuft et al (43)</td>
<td>1</td>
<td>1 incidental</td>
<td>46</td>
<td>SLT</td>
<td>NA</td>
<td>OLB</td>
<td>AR, CMV, BO</td>
<td>RS was diagnosed 26 weeks after LT 46 weeks later re-transplant; RS occurred again</td>
<td></td>
</tr>
<tr>
<td>Carre P et al (55)</td>
<td>1</td>
<td>1 incidental</td>
<td>25</td>
<td>SLT</td>
<td>Cyclosporin Azathioprine Prednisolone</td>
<td>TBLB</td>
<td>AR</td>
<td>SR occurred 24 &amp; 36 months after LT</td>
<td></td>
</tr>
<tr>
<td>Kazerooni EA et al (47)</td>
<td>2</td>
<td>2 incidental</td>
<td>43/44</td>
<td>BLT/HLT</td>
<td>NA</td>
<td>TBLB</td>
<td>1 patient developed ARDS</td>
<td>SR occurred 15 months and 12 months after LT</td>
<td>NA</td>
</tr>
<tr>
<td>Martinez JF et al (48)</td>
<td>1</td>
<td>1 symptomatic</td>
<td>40</td>
<td>BLT</td>
<td>NA</td>
<td>TBLB</td>
<td></td>
<td>SR occurred 13 months after LT</td>
<td></td>
</tr>
<tr>
<td>Yeatman M et al (56)</td>
<td>11</td>
<td>2</td>
<td>45,7</td>
<td>HLT/SLT:5/6</td>
<td>NA</td>
<td>TBLB</td>
<td>CVA Bronchial anastomotic stricture</td>
<td>5 died COD: TB, CMV infection, PTLD</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Incidental</td>
<td>Symptomatic</td>
<td>Time (months)</td>
<td>Type</td>
<td>Immunosuppression</td>
<td>Diagnostic Procedure</td>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
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<td>-------------------</td>
<td>----------------------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martel S et al (45)</td>
<td>1</td>
<td>1 incidental</td>
<td>25</td>
<td>SLT</td>
<td>Cyclosporin, Azathioprine, Prednisone</td>
<td>TBLB</td>
<td>NONE</td>
<td>AR occurred 1 &amp; 2 years after LT RS occurred 22 months after LT 3 years after LT BO</td>
<td></td>
</tr>
<tr>
<td>Kiatboonsri C.et al (57)</td>
<td>1</td>
<td>1 symptomatic</td>
<td>59</td>
<td>BLT</td>
<td>Cyclosporin, Azathioprine, Prednisone</td>
<td>TBLB</td>
<td>NONE</td>
<td>RS occurred 12 &amp; 18 months after LT on each lungs respectively</td>
<td></td>
</tr>
<tr>
<td>Nunley DR et al (46)</td>
<td>9</td>
<td>5 incidental</td>
<td>44.4</td>
<td>SLT</td>
<td>Cyclosporin or Tacrolimus, Azathioprine, Prednisone</td>
<td>TBLB</td>
<td>NA</td>
<td>RS occurred earliest at 21 days, average 224 days after LT COD(n:4): Refractory AR, CMV &amp; aspergillus infection, CNS infection with Nocardia 67% at one year</td>
<td></td>
</tr>
<tr>
<td>Arcasoy SM et al (58)</td>
<td>12</td>
<td>2 incidental</td>
<td>NA</td>
<td>SLT/BLT:4/8</td>
<td>Cyclosporin, Azathioprine, Prednisone</td>
<td>TBLB</td>
<td>NA</td>
<td>5 pts died COD: aspergillus infection (n:3), intraoperative hemorrhage(n:1), hemolytic uremic syndrome 66% at 1 year, 40% at 2 years, and 31% at 3 years</td>
<td></td>
</tr>
<tr>
<td>Ionescu DN et al (40)</td>
<td>NA</td>
<td>8</td>
<td>39-53</td>
<td>SLT/BLT:6/2</td>
<td>NA</td>
<td>TBLB</td>
<td>AR (all)</td>
<td>RS occurred between 6 months to 2 years after LT</td>
<td></td>
</tr>
<tr>
<td>Milman N et al (59)</td>
<td>7</td>
<td>3</td>
<td>51</td>
<td>SLT</td>
<td>Cyclosporin, Azathioprine, Prednisone</td>
<td>TBLB</td>
<td>BOS (1): died</td>
<td>RS occurred 1-6 months after LT</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>No.</td>
<td>Incidental</td>
<td>Incidence (%)</td>
<td>Type</td>
<td>Recurrence Treatment</td>
<td>TBLB</td>
<td>RS Occurrence Time</td>
<td>Survival After LT (Years)</td>
<td>Remarks</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----</td>
<td>------------</td>
<td>---------------</td>
<td>------</td>
<td>----------------------</td>
<td>------</td>
<td>-------------------</td>
<td>------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Banga A et al (41)</td>
<td>30</td>
<td>7</td>
<td>50.7</td>
<td>SLT:5 BLT:24 HLT:1</td>
<td>Either tacrolimus or cyclosporin, mycophenolate mofetil or Azathioprine and prednisone</td>
<td>TBLB</td>
<td>RS occurred between 6 weeks to 12 months after LT AR was seen lower in RS pts</td>
<td>1-year, 3-year, and 5-year survival was 80%, 63.3%, and 50%, respectively. RS had no impact on survival</td>
<td></td>
</tr>
<tr>
<td>Collins J et al (31)</td>
<td>26</td>
<td>9</td>
<td>40-59</td>
<td>SLT:3 BLT:5 HLT:1</td>
<td>NA</td>
<td>TBLB</td>
<td>NA</td>
<td>RS occurred between 3 to 24 months after LT</td>
<td></td>
</tr>
<tr>
<td>Le Pavec J et al (38)</td>
<td>112</td>
<td>11</td>
<td>52</td>
<td>SLT:8 BLT:101 HLT:3</td>
<td>NA</td>
<td>TBLB</td>
<td>PGD:24 Hemorrhax:16</td>
<td>36 pts died COD: CLAD:14, infection:9, bleeding:2, sudden death:2, multiple organ failure:2, cancer:1, PGD:1, other:3 3 pts underwent re-tx RS occurred usually in 24 months</td>
<td>5-year survival was 69%</td>
</tr>
</tbody>
</table>

Table 3. The features of recurrence of Pulmonary Langerhans cell histiocytosis following Lung Transplantation

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No of tx/no R-PLCH</th>
<th>Pre-tx symptoms</th>
<th>Mean age</th>
<th>Type of tx</th>
<th>Post-transp. IS drugs</th>
<th>DX</th>
<th>Post-transp. complications</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabbay et al (69)</td>
<td>1</td>
<td>DI at age 12, no smoking, restr PFT, reduced DLCO, PHT</td>
<td>32</td>
<td>BLT</td>
<td>cyclosporin Azathioprine Prednisolone</td>
<td>TBLB</td>
<td>NONE</td>
<td>24 and 30 months after tx R-PLCH occurred</td>
</tr>
<tr>
<td>Habib et al (70)</td>
<td>1</td>
<td>R-PNX</td>
<td>28</td>
<td>blt</td>
<td>cyclosporin azathioprine prednisolone</td>
<td>TBLB</td>
<td>CMV &amp; P. aeruginosa pneumonia</td>
<td>11 months after tx R-PLCH occurred</td>
</tr>
<tr>
<td>Etienne et al (71)</td>
<td>Case 1</td>
<td>Smoker, dyspnea, a cough, weight loss, fatigue, PFT: obstructive, and oxygen desaturation on exercise</td>
<td>21</td>
<td>SLT</td>
<td>cyclosporin azathioprine prednisolone</td>
<td>TBLB</td>
<td>CMV</td>
<td>12 months after tx R-PLCH occurred (resumed smoking)</td>
</tr>
<tr>
<td>Case 2</td>
<td>Smoker, DI &amp; R-PNX</td>
<td>31</td>
<td>SLT</td>
<td>cyclosporin azathioprine prednisolone</td>
<td>TBLB</td>
<td>septicemia due to Staphylococcus aureus and severe hyponatremia due to desmopressin abuse</td>
<td>12 months after tx R-PLCH occurred (resumed smoking)</td>
<td></td>
</tr>
<tr>
<td>Collins et al (31)</td>
<td>4/1</td>
<td>NON-SMOKER</td>
<td>21</td>
<td>NA</td>
<td>NA</td>
<td>TBLB</td>
<td>NA</td>
<td>7 months after tx R-PLCH occurred</td>
</tr>
<tr>
<td>Dauria et G et al (72)</td>
<td>39/8</td>
<td>Nonsmoker:2, current smoker:1, former smoker:35</td>
<td>38,5</td>
<td>SLT:15, BLT:15, HLT:9</td>
<td>NA</td>
<td>3: CT, 4: TBLB, 1: SLB</td>
<td>NA</td>
<td>Recurrence was seen between 12-60months COD: 1 pneumonia, 1 lung cancer, 1 morphine overdose 3 pts resumed smoking</td>
</tr>
</tbody>
</table>

### Table 4. Recurrence of hard metal lung disease following Lung Transplantation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Ref.</th>
<th>Year</th>
<th>No. of patients</th>
<th>Type of transplant</th>
<th>Age at transplant (yr.)</th>
<th>Time to relapse</th>
<th>Post-transplant complications</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hard metal lung</td>
<td>Tarabichi et al (78)</td>
<td>2015</td>
<td>1</td>
<td>Single left</td>
<td>45</td>
<td>900 days</td>
<td>Grade A2 rejection, 3 episodes of lung injury</td>
<td>exitus</td>
</tr>
<tr>
<td></td>
<td>Frost et al (79)</td>
<td>1993</td>
<td>1</td>
<td>single</td>
<td>NA</td>
<td>2 years</td>
<td>NA</td>
<td>exitus</td>
</tr>
</tbody>
</table>
Table 5. Recurrence of Emphysema following Lung Transplantation among patients with Alpha1 Anti-Trypsin Deficiency

<table>
<thead>
<tr>
<th>Disease</th>
<th>Ref.</th>
<th>Year</th>
<th>No. of patients</th>
<th>Type of transplant</th>
<th>Age at transplantation (yr)</th>
<th>Time to relapse</th>
<th>Post-transplant complications</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AATD</td>
<td>Mal H. et al (86)</td>
<td>2004</td>
<td>1</td>
<td>Single right</td>
<td>50</td>
<td>11 years</td>
<td>Acute lung rejection episodes</td>
<td>Dyspnea, FEV 52% predicted</td>
</tr>
<tr>
<td></td>
<td>Ataya A (87)</td>
<td>2020</td>
<td>1</td>
<td>bilateral</td>
<td>59</td>
<td>2 years</td>
<td>NA</td>
<td>Alive, receiving AAT treatment</td>
</tr>
</tbody>
</table>
### Table 6. Recurrence of Pulmonary Alveolar Proteinosis following Lung Transplantation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Ref.</th>
<th>Year</th>
<th>No. of patients</th>
<th>Type of transplant</th>
<th>Age at transplant (yr)</th>
<th>Post-transplant complications</th>
<th>Outcomes</th>
<th>Genetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAP</td>
<td>Parker et al (94)</td>
<td>1997</td>
<td>1</td>
<td>Bilateral</td>
<td>41</td>
<td>Mild obliterative bronchiolitis</td>
<td>Recurrence of disease after 3 years</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Santamaria et al. (95)</td>
<td>2004</td>
<td>1</td>
<td>Heart*lung transplant</td>
<td>3</td>
<td>EBV infection</td>
<td>Died 26 months after tx</td>
<td>SLC7A7 gene mutation causing lysinuric protein intolerance</td>
</tr>
<tr>
<td></td>
<td>Takaki et al (96)</td>
<td>2016</td>
<td>1</td>
<td>Bilateral</td>
<td>36</td>
<td>Dyspnea at 9th month</td>
<td>Recurrence of PAP at 16th month, exitus</td>
<td>Nonsense mutation in CSF2RB</td>
</tr>
</tbody>
</table>
**Table 7. Recurrence of Interstitial lung disease following Lung Transplantation**

<table>
<thead>
<tr>
<th>Type of ILD Disease</th>
<th>Ref.</th>
<th>Year</th>
<th>No. of patients</th>
<th>Type of transplant</th>
<th>Age at transplantation (yr)</th>
<th>Post-transplant complications</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIP</td>
<td>King et al (107)</td>
<td>1997</td>
<td>1</td>
<td>Left single</td>
<td>52</td>
<td>Cytomegalovirus and Nocardia infections</td>
<td>Recurrence after 1 month and death at 8th month</td>
</tr>
<tr>
<td>DIP</td>
<td>Verleden et al (108)</td>
<td>1998</td>
<td>1</td>
<td>Left single</td>
<td>51</td>
<td>Grade A2 rejection, Pneumocystis carinii pneumonia</td>
<td>Recurrence after 1 year and good recovery</td>
</tr>
<tr>
<td>DIP</td>
<td>Kotecha et al (109)</td>
<td>2019</td>
<td>1</td>
<td>Bilateral</td>
<td>59</td>
<td>Antibody mediated rejection, cytomegalovirus and aspergillus pneumonia</td>
<td>Recurrence after 14 months</td>
</tr>
<tr>
<td>NSIP</td>
<td>Bhatt et al (110)</td>
<td>2010</td>
<td>1</td>
<td>Bilateral</td>
<td>42</td>
<td>Grade 3 PGD, HIT, DVT, grade A2B0 rejection</td>
<td>Recurrence after several months</td>
</tr>
<tr>
<td>HP</td>
<td>Kern et al (111)</td>
<td>2013</td>
<td>1</td>
<td>Bilateral</td>
<td>49</td>
<td>NA</td>
<td>Recurrence after 3 years</td>
</tr>
<tr>
<td>PM-ILD</td>
<td>Arboleda et al (112)</td>
<td>2014</td>
<td>1</td>
<td>Bilateral</td>
<td>15</td>
<td>NA</td>
<td>Recurrence at 9th month and death</td>
</tr>
<tr>
<td>NSIP-F</td>
<td>Scallan et al (113)</td>
<td>2020</td>
<td>1</td>
<td>Bilateral</td>
<td>52</td>
<td>Grade A3 rejection</td>
<td>Recurrence after 30 months</td>
</tr>
</tbody>
</table>
Table 8. Recurrence of Idiopathic Pulmonary Hemosiderosis following Lung Transplantation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Ref.</th>
<th>Year</th>
<th>No. of patients</th>
<th>Type of transplant</th>
<th>Age at transplantation (yr.)</th>
<th>Time to relapse</th>
<th>Post-transplant complications</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPH</td>
<td>Calabrese et al (118)</td>
<td>2002</td>
<td>1</td>
<td>Bilateral</td>
<td>36</td>
<td>3 years</td>
<td>A2 rejection</td>
<td>Recovery after augmentation of steroid treatment</td>
</tr>
<tr>
<td></td>
<td>Ross et al (119)</td>
<td>2020</td>
<td>1</td>
<td>Bilateral</td>
<td>26</td>
<td>1.5 years</td>
<td>Severe PGD requiring ECMO, pulmonary syphilis</td>
<td>Alive, stable disease</td>
</tr>
</tbody>
</table>
Table 9. Recurrence of Bronchoalveolar Carcinoma following Lung Transplantation

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. of transpl</th>
<th>No. of RS</th>
<th>Type of tx</th>
<th>Post-transp. complications</th>
<th>Outcomes</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perrot et al (121)</td>
<td>26</td>
<td>13</td>
<td>SLT:8, BLT:17, HLT:1</td>
<td>4 died post-op</td>
<td>9 of them died between 11 and 82 months from respiratory failure</td>
<td>5-year survival was 39%</td>
</tr>
<tr>
<td>Zorn et al (122)</td>
<td>8</td>
<td>6</td>
<td>SLT: 2, BLT: 6, 1re-tx BLT</td>
<td>3 patients died because of progressive pulmonary failure and cerebral edema</td>
<td>Recurrence free for 2 patients</td>
<td>Survival of 87 and 76 months for recurrence free patients</td>
</tr>
<tr>
<td>Shin et al (123)</td>
<td>6</td>
<td>3</td>
<td>BLT</td>
<td>Recurrence at 10, 39 and 48 months</td>
<td>Similar radiological and histological features with primary tumor</td>
<td>Alive</td>
</tr>
<tr>
<td>Garver et al (124)</td>
<td>7</td>
<td>4</td>
<td>BLT:5, SLT:2</td>
<td>Recurrence from 10 to 48 months</td>
<td>Similar histological and molecular features</td>
<td>1 patient who had re-tx died 9 months after LT</td>
</tr>
<tr>
<td>Gomez-Roman et al (125)</td>
<td>1</td>
<td>1</td>
<td>BLT</td>
<td>Recurrence after 35 months</td>
<td>3 pulmonary wedge resections were performed for recurrence</td>
<td>NA</td>
</tr>
</tbody>
</table>
### Table 10. Recurrence of Diffuse Pan Bronchiolitis following Lung Transplantation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Ref.</th>
<th>Year</th>
<th>No. of patients</th>
<th>Type of transplant</th>
<th>Age at transplant (yr.)</th>
<th>Post-transplant complications</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPB</td>
<td>Baz MA et al (130)</td>
<td>1995</td>
<td>1</td>
<td>Bilateral</td>
<td>NA</td>
<td>Recurrence of disease after 10 weeks</td>
<td>Improvement of allograft function with erythromycin</td>
</tr>
<tr>
<td></td>
<td>Chen F et al (128)</td>
<td>2015</td>
<td>2</td>
<td>Bilateral</td>
<td>35</td>
<td>Recurrence after 4 months, pseudomonas and CMV infection</td>
<td>Death after 6 years</td>
</tr>
<tr>
<td>Disease</td>
<td>Ref.</td>
<td>Year</td>
<td>No. of patients</td>
<td>Type of transplant</td>
<td>Age at transplantation (yr.)</td>
<td>Time to relapse</td>
<td>Post-transplant complications</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-----------------------</td>
<td>------</td>
<td>-----------------</td>
<td>--------------------</td>
<td>-----------------------------</td>
<td>-----------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Pulmonary capillary hemangiomatosis</td>
<td>Lee et al. (133)</td>
<td>2010</td>
<td>1</td>
<td>Bilateral</td>
<td>52</td>
<td>8 months</td>
<td>Organizing pneumonia, bronchitis, small airway dysfunction</td>
</tr>
<tr>
<td>Idiopathic pulmonary arterial hypertension</td>
<td>Narula et al. (131)</td>
<td>2014</td>
<td>1</td>
<td>Bilateral</td>
<td>62</td>
<td>1 year</td>
<td>Recurrence of pulmonary hypertension and right heart failure</td>
</tr>
<tr>
<td>Pulmonary veno-occlusive disease</td>
<td>Izbicki et al. (132)</td>
<td>2005</td>
<td>1</td>
<td>Heart and lung tx</td>
<td>28</td>
<td>3 months</td>
<td>NA</td>
</tr>
<tr>
<td>Epithelioid hemangioendothelioma</td>
<td>Desie et al. (134)</td>
<td>2015</td>
<td>1</td>
<td>Liver and lung tx</td>
<td>45</td>
<td>4 months</td>
<td>Bronchiolitis obliterans syndrome</td>
</tr>
</tbody>
</table>