Radiology: Cardiothoracic Imaging

REVIEW

Complications of Lung Transplantation: Update on Imaging Manifestations and Management

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As lung transplantation has become the most effective definitive treatment option for end-stage chronic respiratory diseases, yearly rates of this surgery have been steadily increasing. Despite improvement in surgical techniques and medical management of transplant recipients, complications from lung transplantation are a major cause of morbidity and mortality. Some of these complications can be classified on the basis of the time they typically occur after lung transplantation, while others may occur at any time. Imaging studies, in conjunction with clinical and laboratory evaluation, are key components in diagnosing and monitoring these conditions. Therefore, radiologists play a critical role in recognizing and communicating findings suggestive of lung transplantation complications. A description of imaging features of the most common lung transplantation complications, including surgical, medical, immunologic, and infectious complications, as well as an update on their management, will be reviewed here.

Supplemental material is available for this article.

Despite the increasing numbers of lung transplantations that are being performed, the median survival of lung transplant recipients between 2009 and 2016 was 6.5 years (1). Improved surgical techniques and early postoperative care have contributed to improved short-term survival. Unfortunately, long-term survival has remained stagnant. This is largely due to the lack of efficacious treatments for chronic lung allograft dysfunction (CLAD), which affects more than 50% of lung transplant recipients 5 years after the operation (2).

Both the prevalence of lung transplantation and our understanding of chronic complications have grown considerably in the past decade. Imaging studies are essential in the clinical evaluation of lung transplant recipients. In this article, we aim to provide an up-to-date and comprehensive review of the imaging features of lung transplantation complications and to provide information on management of these complications, which is of high interest for radiologists and clinicians.

Surgical Complications

Size Mismatch

While small differences in donor lungs and recipient thorax size are acceptable, substantial size mismatches have been associated with clinical symptoms, abnormal radiographic findings, and bronchiolitis obliterans incidence (3,4). Size mismatches between the donor and recipient can be directly observed at the time of surgery. After surgery, size mismatch is a potential cause of airway flow limitation and restrictive physiology, which can be monitored with spirometry. Radiographic findings suggestive of lung size mismatch include atelectasis when donor lungs are too large and recurrent pleural effusion and pneumothorax when donor lungs are too small (5). To prevent size mismatch, lobectomy (usually right middle lobe or lingula) can be performed on the donor lungs to have a better size-matched transplantation (3).

Anastomotic Complications of Pulmonary Vasculature

Anastomotic complications of pulmonary vasculature include pulmonary venous stenosis and thrombosis, pulmonary arterial stenosis, and torsion of the bronchovascular pedicle.

Vascular complications are more common in patients with small chest cavities and fibrotic disease (6). Deaths due to pulmonary artery and pulmonary vein stenosis have been reported in transplant recipients, but mortality rates remain under investigation (6). Torsion of the bronchovascular pedicle is rare, however, it may lead to graft loss if not recognized expeditiously (7,8).

Pulmonary venous stenosis and thrombosis have an incidence of 1%–15% in patients who have undergone lung transplantation and occur in the first 24–48 hours following surgery (6,9). Clinical signs include pulmonary edema and venous congestion. Pulmonary artery complications have an incidence of 2% and typically occur within 2 weeks following lung transplantation (6,9). Signs of pulmonary artery stenosis include unexplained hypoxia and pulmonary hypertension. Torsion is a rare entity described mainly in case reports and small case series and has been described to be recognized 1 to 4 days following

Abbreviations

ACR = acute cellular rejection, AFOP = acute fibrosis and organizing pneumonia, AMR = antibody-mediated rejection, ARAD = azithromycin-responsive allograft dysfunction, BOS = bronchiolitis obliterans syndrome, CLAD = chronic lung allograft dysfunction, FEV_1 = forced expiratory volume in 1 second, HLA = human leukocyte antigen, OB = obliterative bronchiolitis, PGD = primary graft dysfunction, PTLD = posttransplant lymphoproliferative disease, RAS = restrictive allograft syndrome, TBM = tracheobronchomalacia

Summary

Considering the steadily increasing rate of lung transplantation surgeries, it is crucial for radiologists to understand imaging manifestations of common complications of this surgery to contribute to multidisciplinary approaches for managing and treating these patients.

Essentials

- Vascular complications such as pulmonary venous stenosis, pulmonary venous and arterial thrombosis, and vascular torsion occur in the early postoperative period and are associated with high morbidity and mortality. CT angiography is a powerful tool for early detection of vascular complications, which is essential for optimizing the outcomes.
- Chronic lung allograft dysfunction is the primary limiting factor of long-term survival in patients who have undergone lung transplantation and represents a heterogeneous group of diseases. It is essential for radiologists to understand imaging features associated with bronchiolitis obliterans syndrome and restrictive allograft syndrome, which are the primary types of chronic lung allograft dysfunction.
- Airway anastomosis complications, including bronchial dehiscence and stenosis, are common and warrant extra attentiveness during image interpretation.

Keywords

Pulmonary, Thorax, Surgery, Transplantation

transplantation. In these case reports, signs of torsion include hypoxia, difficulty weaning from ventilator, and serosanguinous secretions at bronchoscopy (7,8).

A high index of suspicion and early investigation with cross-sectional imaging is essential for the diagnosis of vascular complications. Transesophageal echocardiography can demonstrate vasculature velocity and size intraoperatively and postoperatively, but it is heavily operator dependent (9). CT angiography allows for better visualization of the pulmonary vasculature and detection of complications. Findings of arterial and venous stenosis may manifest as focal narrowing of vasculature (with or without poststenotic dilatation), and thrombosis may appear as an intraluminal filling defect (9) (Figs 1, 2). Folds measuring 1–2 mm on the wall of the arteries and veins at the sites of anastomosis without a substantial reduction in diameter are normal findings and should not be interpreted as vascular anastomosis stenosis (9). Indirect lung parenchymal findings suggestive of pulmonary artery or venous stenosis include ground-glass opacities or consolidations with or without interlobular septal thickening in the associated lobes (Fig 1). Parenchymal findings are particularly helpful for identifying pulmonary vein complications, as these vessels are not optimally opacified at CT angiography (9). Swirling or aberrant course of bronchi and vessels on CT angiographic images are findings suggestive of bronchovascular torsion (7,8) (Fig 3).

Treatment of vascular complications depends on the severity of the graft dysfunction and multidisciplinary discussion between radiologists, surgeons, transplant intensivists, and interventional vascular teams. Options range from close monitoring to surgical correction. Angioplasty with or without stent placement can be considered in more clinically stable patients diagnosed weeks after transplantation (10). The risk of anastomotic dehiscence with intravascular interventions is a limiting factor.

Bronchial Dehiscence

The preferred method of native to allograft bronchial anastomosis is an end-to-end running suture approach close to the first lobar takeoff (11). Despite progress in surgical techniques, airway anastomotic complications affect approximately one in five lung transplant recipients and carries a mortality rate of 2%–4% (12). The most common airway anastomotic complications are bronchial dehiscence and bronchial stenosis. The latter will be discussed in the next section. The prevalence of bronchial dehiscence is 1%–10% in lung transplant recipients and typically occurs 2–4 weeks after transplantation (13). The donor lung bronchi are susceptible to ischemia due to lack of bronchial and pulmonary collateral circulation. Ischemia can lead to bronchial wall injury, tissue necrosis, and, in severe cases, disruption of anastomosis (dehiscence) (14). Risk factors that have been associated with bronchial dehiscence are infection and acute rejection (15).

Clinical presentations of bronchial dehiscence are dyspnea, persistent air leak, and inability to wean from mechanical ventilation (12). When bronchial dehiscence is asymptomatic, imaging and bronchoscopy are essential for diagnosis. CT findings of bronchial dehiscence are bronchial wall irregularity and wall defects (Fig 4). In mild cases, bronchial wall irregularity may not be discernable at imaging. Ancillary findings of bronchial dehiscence are pneumomediastinum, pneumothorax, and lung collapse (14). These indirect findings must be interpreted with caution, as they can be observed in the early postoperative period and in the presence of mediastinal drains and chest tubes. It is appropriate to question bronchial dehiscence when these findings are persistent or unexplained. When bronchial dehiscence is suspected, direct visualization with bronchoscopy is the definitive test for diagnosis (12).

Bronchial dehiscence is treated by mitigating risk factors and managing the anastomotic defect. The latter includes placement of chest tubes to allow for lung expansion, deployment of airway stents to decrease air leaks and induce granulation and healing, and application of fibrin and cyanoacrylate glue for small leaks (16). Severe cases are treated with bronchoplasty and flaps (12,16). The use of growth factors has also been described but remains experimental (16).

Bronchial Stenosis

Bronchial stenosis is the most common airway complication and affects 4%–24% of lung transplant recipients (17). It typically occurs 2–9 months after lung transplantation, and the

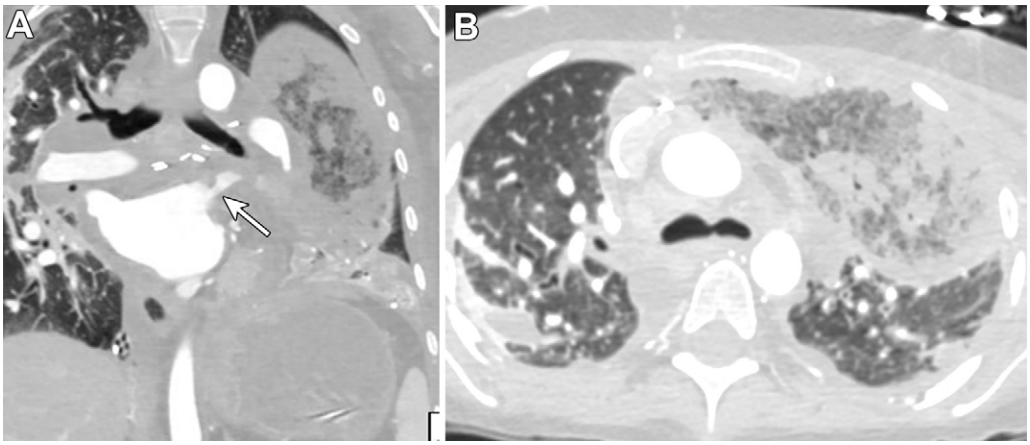

Figure 1: Images in a 49-year-old man with left pulmonary vein stenosis identified 1 week after bilateral lung transplantation for cystic fibrosis. **(A)** Coronal chest CT bone window image shows stenosis of the left upper lobe pulmonary vein (arrow), and **(B)** axial chest CT image shows left upper lobe consolidation and ground-glass opacities due to pulmonary venous congestion and likely venous infarction.

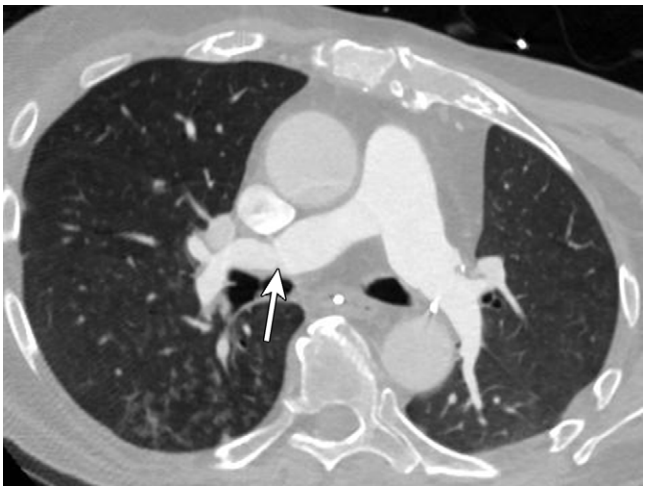

Figure 2: Image in a 58-year-old man with pulmonary artery stenosis identified at the first postoperative CT performed after bilateral lung transplantation for interstitial lung disease. Three-dimensional reconstructed axial chest CT image shows stenosis of the right main pulmonary artery (arrow) with relative lucency and hypovascularity of the right lung in the setting of right main pulmonary artery stenosis.

mean survival is 22–82 months depending on the treatment approach (17). Risk factors are bronchial ischemia, history of primary graft dysfunction (PGD), acute allograft rejection, anastomotic infection, and anastomotic dehiscence (15,18). Much like bronchial dehiscence, the incidence of bronchial stenosis is declining with improvement of surgical techniques and the use of end-to-end anastomosis with a running suture (11). Bronchial stenosis can be asymptomatic or manifest with symptoms of dyspnea, cough, recurring postobstructive pneumonia, wheezing, and increased obstruction on pulmonary function tests (17). Clinically significant stenosis is described as greater than 50% bronchial luminal narrowing and can be diagnosed bronchoscopically or with CT (14) (Fig 5).

The management of bronchial stenosis depends on the severity, which is graded by the degree of narrowing. Multiplanar reformatted CT images provide better understanding of the degree of bronchial stenosis with high degree of agreement with bronchoscopy (19). Mild stenosis (less than 50% lumen narrowing) is managed by clinical follow-up and repeat bronchoscopy. Stenosis with greater than 50% narrowing can be treated with balloon dilation (14). After two to three balloon dilations, stent placement can be considered (20). Silicone stents are favored, as they induce less granulation tissue and are easier to remove than metal and hybrid stents (20). Other treatments that have been used on a case-by-case basis include injection of mitomycin, laser treatments, brachytherapy, and local steroid injections (20).

Chest Wall and Pleural Complications

Lung transplantation can be performed by a sternotomy incision, a bilateral anterolateral thoracotomy, or a continuous horizontal incision with sternal disruption (clamshell incision) (21). Chest wall complications occur days to weeks following lung transplantation and include hemothorax, extrathoracic hematoma, wound dehiscence, and wound infection.

The prevalence of hemothorax is 12%–18% in lung transplant recipients, and anticoagulation is a risk factor (22). Postoperative hemothorax has been associated with reduced survival and has been cited as a direct cause of death in lung transplant recipients (22,23). Clinical signs of hemothorax are sanguineous chest tube output and decrease in hematocrit level. At CT, hemothorax manifests as pleural effusions with attenuation suggestive of blood products (35–70 HU) (23). Anticoagulation is also a risk factor for extrathoracic hematomas, which can occur spontaneously or as a result of misplaced lines and tubes (24). Extrathoracic hematomas can be seen at physical examination and further evaluated with US or CT imaging (Fig 6). Treatment depends on severity and may require surgical intervention in severe cases.

Wound dehiscence and wound infection occur in up to 2% of lung transplant recipients. Mediastinitis occurs when there is direct extension of infection into the mediastinum and carries a mortality rate of 29% in transplant recipients (25). Wound dehiscence can be observed at physical examination. Wound infection with or without mediastinitis can be suspected in patients

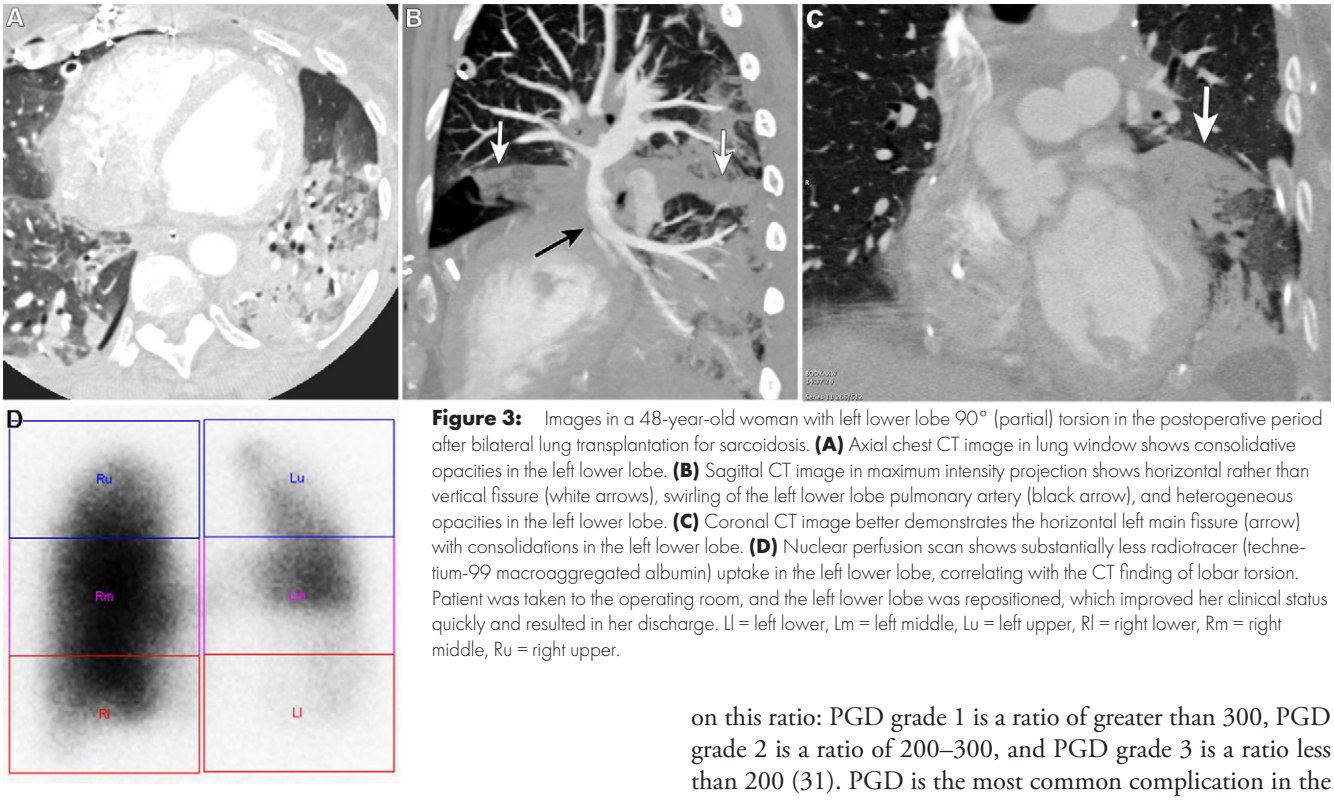

Figure 3: Images in a 48-year-old woman with left lower lobe 90° (partial) torsion in the postoperative period after bilateral lung transplantation for sarcoidosis. **(A)** Axial chest CT image in lung window shows consolidative opacities in the left lower lobe. **(B)** Sagittal CT image in maximum intensity projection shows horizontal rather than vertical fissure (white arrows), swirling of the left lower lobe pulmonary artery (black arrow), and heterogeneous opacities in the left lower lobe. **(C)** Coronal CT image better demonstrates the horizontal left main fissure (arrow) with consolidations in the left lower lobe. **(D)** Nuclear perfusion scan shows substantially less radiotracer (technetium-99 macroaggregated albumin) uptake in the left lower lobe, correlating with the CT finding of lobar torsion. Patient was taken to the operating room, and the left lower lobe was repositioned, which improved her clinical status quickly and resulted in her discharge. Ll = left lower, Lm = left middle, Lu = left upper, Rl = right lower, Rm = right middle, Ru = right upper.

presenting with fever and leukocytosis. Imaging becomes a crucial tool in guiding treatment in these patients because it may be difficult to recognize the clinical degree of mediastinal involvement. CT findings of mediastinal involvement include pneumomediastinum, obliteration of fat planes, mediastinal fat stranding, and abscess formation (26). PET/CT with fluorodeoxyglucose and gallium 67 scintigraphy are also valuable in determining presence of mediastinitis, with sensitivity of 78% and 83% and specificity of 82% and 96%, respectively (27,28). Treatment of chest wall infection depends on its extent and severity. Early or mild infection can be treated with antibiotics. Wound cultures, including *Mycobacterium abscessus* and *Mycoplasma* and/or *Ureaplasma* cultures, are essential for tailoring treatment. Advanced disease requires surgical debridement. Occasionally, a vacuum-assisted closure or omental flap is needed (29). Surgical complications and their imaging findings are summarized in Table 1.

Medical Complications

Primary Graft Dysfunction

PGD is a multifactorial process leading to acute lung injury, which occurs 24–72 hours after lung transplantation. PGD has substituted other terms to describe this process, including *reperfusion*, *edema*, *primary graft failure*, and *early graft dysfunction* (30). PGD has been defined by the International Society for Heart and Lung Transplantation as diffuse alveolar opacities on radiographs and hypoxemia on the basis of the ratio of arterial oxygen partial pressure in millimeters of mercury to fractional inspired oxygen (pO2/FiO2). PGD severity is based on this ratio: PGD grade 1 is a ratio of greater than 300, PGD grade 2 is a ratio of 200–300, and PGD grade 3 is a ratio less than 200 (31). PGD is the most common complication in the early postoperative period (31). It affects 10%–25% of lung transplant recipients and accounts for approximately 49% of deaths at 30 days after surgery (32).

PGD is a complex multifactorial process. The central process implicated in PGD is direct injury to the lung graft during organ collection and implantation. This leads to formation of toxic reactive oxygen species that trigger host inflammatory and immunologic responses (33). Understanding this physiology is essential for identifying risk factors that can be donor related, recipient related, or surgical. These are summarized in Table 2 (33–35).

Signs and symptoms of PGD are similar to acute respiratory distress syndrome (32). PGD is suspected when patients develop hypoxia with no other identifiable cause. CT manifestations of PGD include diffuse ground-glass opacities, interlobular septal thickening, and bronchial wall thickening predominantly involving middle and lower lobes (36,37). These findings peak in the first 24 hours after transplantation and usually resolve by 14 days (37). Although CT findings are not specific, the lobar predominance and timing are helpful clues in distinguishing this entity from pulmonary edema, infection, or allograft rejection.

Prevention of PGD is focused on mitigating risk factors. The management of PGD is similar to the management of acute respiratory distress syndrome. Protective lung ventilation allows for the alveoli to heal, and inhaled nitric oxide can be used to correct ventilation-perfusion mismatch and lower pulmonary artery pressure (35). When conservative treatments fail, extracorporeal membrane oxygenation is used (35).

Pulmonary Embolism and Deep Vein Thrombosis

Thromboembolic disease, including deep venous thrombosis and pulmonary embolism, has an increased incidence in

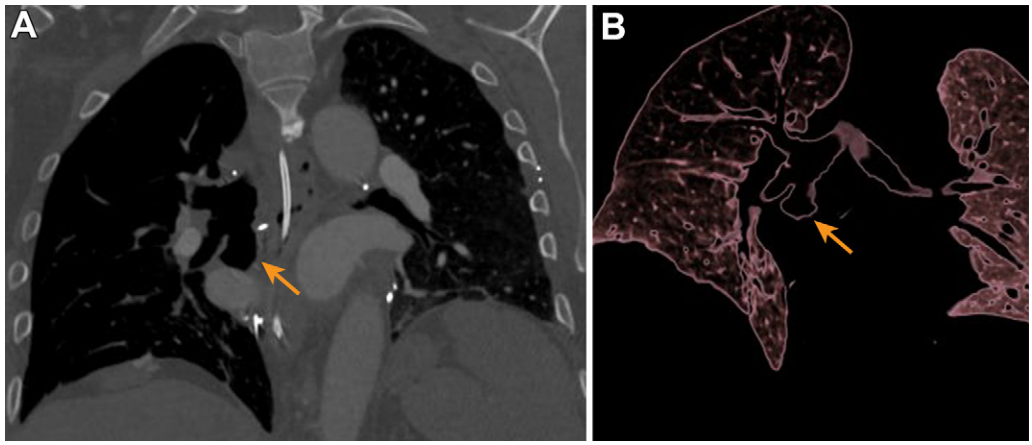

Figure 4: Images in a 48-year-old man with bronchial dehiscence 1 month after bilateral lung transplantation for idiopathic pulmonary fibrosis. **(A)** Coronal chest CT three-dimensional reconstructed minimum intensity projection image and **(B)** volume-rendered reformat image show outpouching (orange arrow) arising from inferior aspect of the bronchus intermedius adjacent to the surgical clips, compatible with bronchial dehiscence. Bronchial dehiscence was managed with endobronchial stent placement.

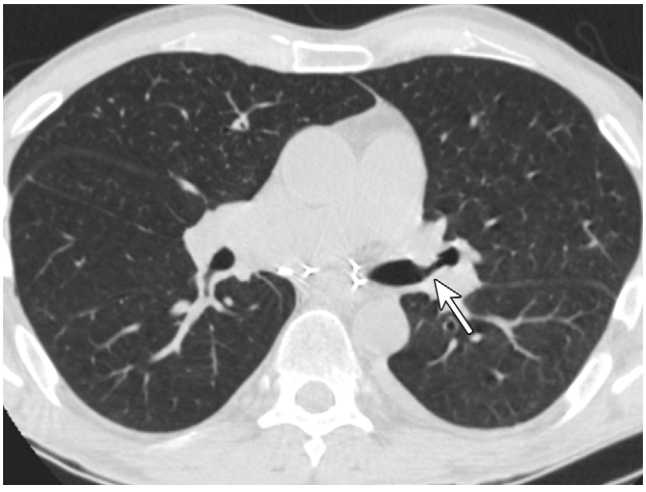

Figure 5: Image in a 52-year-old man with left bronchial stenosis after bilateral lung transplantation for end-stage chronic obstructive pulmonary disease. Axial chest CT lung window image shows focal narrowing of the left mainstem bronchus (arrow) 2 months after lung transplantation.

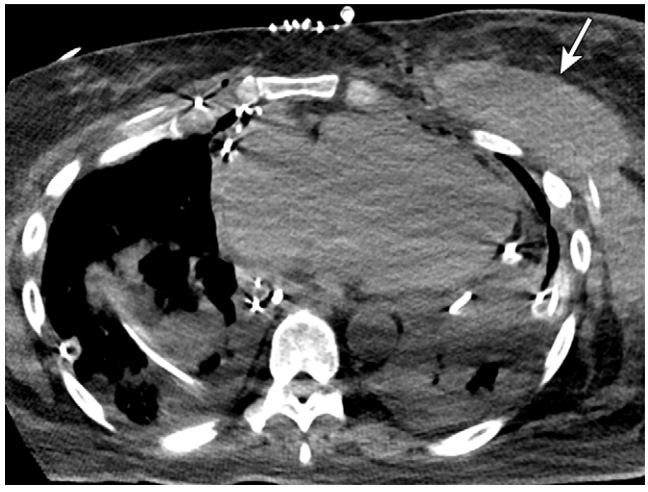

Figure 6: Image in a 62-year-old woman with chest wall hematoma 2 weeks after bilateral lung transplantation for interstitial lung disease. Axial chest CT image shows fluid collection in the soft tissues of the left chest wall, measuring 45 HU on average, consistent with chest wall hematoma. Hematoma resolved in 2 weeks after surgical drain placement.

lung transplant recipients, with rates of 8.6%–26% cited in the literature (38–40). Multiple studies have identified thromboembolic disease as an independent contributor to mortality in lung transplant recipients (41,42). Risk factors include obesity, immobility, advanced age, and indwelling catheters (43). Additionally, lung transplant recipients are at increased risk for pulmonary infarction due to absent and underdeveloped collateral circulation (43). Deep venous thrombosis and pulmonary embolism can occur at any time after lung transplantation.

Pulmonary embolism is associated with tachycardia and presence of deep venous thrombosis, and symptoms include dyspnea, cough, and hemoptysis. Pulmonary embolisms will appear as arterial filling defects or abrupt arterial cutoff at CT angiography. Other findings include oligemia and wedge-shaped peripheral consolidation or ground-glass opacity suggestive of pulmonary infarct (24). Pulmonary embolisms are managed with mitigation of risk factors and anticoagulation.

Tracheobronchomalacia

Historically, tracheobronchomalacia (TBM) has been defined as greater than 50% luminal narrowing at expiration. More recent data have shown that this degree of bronchial narrowing during expiration can be physiologic and is often seen in healthy volunteers (44). Therefore, identifying severe cases of luminal narrowing (defined as greater than 90% with expiration) while considering relevant clinical symptoms may be a more effective way to diagnose this disease (44). While 1%–4% of lung transplant recipients receive a diagnosis of TBM, the variability of its definition precludes accurate assessment of its prevalence (17). TBM is related to the loss of muscle and cartilaginous support, which can occur as a consequence of ischemia, chronic rejection, and bronchial stenosis (45). It typically occurs 2–4 months after lung transplantation and can occur anywhere in the lung graft, including the perianastomotic region and postanastomotic airways (17,24).

Table 1: Surgical, Medical, and Immunologic Complications of Lung Transplantation

Complication	Timing Following Surgery	Imaging Feature	Reference
Surgical complication			
Size mismatch	Immediate	Atelectasis Pleural effusions Pneumothorax	(5)
Vascular anastomosis			
Venous stenosis	Hours to days	Focal narrowing, poststenotic dilatation	(9)
Arterial stenosis	Days to weeks	Focal narrowing, poststenotic dilatation	
Pulmonary torsion	Hours to days	Swirling course of bronchi and vasculature	(7,8)
Bronchial dehiscence	Days to weeks	Bronchial wall irregularity and defects Persistent unexplained pneumothorax and pneumomediastinum	(14)
Bronchial stenosis	2–9 months	Luminal narrowing (with respect to normal bronchial diameter)	(19)
Hemothorax	Days to weeks	Fluid collections and pleural effusion with blood attenuation	(23)
Chest wall infection with mediastinal involvement	Days to weeks	Fat stranding Obliteration of fat planes Mediastinal fluid Mediastinal gas	(26)
Medical complication			
Primary graft dysfunction	Hours to days	Ground-glass opacities Interlobular septal thickening Bronchial wall thickening	(36,37)
Pulmonary embolism	Anytime	Pulmonary artery filling defect Wedge-shape peripheral consolidation or ground-glass opacities	(24)
Tracheobronchomalacia	2–4 months	Luminal narrowing (during expiration compared with inspiration)	(14)
PTLD	1 month–anytime thereafter	Single or multiple homogeneously attenuating nodules Fluorodeoxyglucose PET/CT avidity	(46,49)
Primary disease recurrence	Months to years	Findings suggestive of original disease (ie, granulomas for sarcoid)	(50)
Lung cancer	Anytime	Growing nodules or masses	(56)
Immunologic complication			
Hyperacute	Minutes to hours		
HLA-ABO incompatibility		Diffuse consolidative opacities Rapid progression is a distinguishing feature	(61,62)
Acute	Weeks to months		
ACR		Volume loss Pleural and septal thickening Pleural effusion Improvement with steroids	(72)
AMR		Ground-glass opacities Air trapping at expiratory thin-section CT	(72)

Table 1 (*continues*)

Symptoms of TBM are cough, dyspnea, stridor, and wheezing. Patients with TBM experience higher rates of mucus plugging and infection (44). On pulmonary function tests, TBM is associated with an obstructive pattern of reduction in lung function (14). Dynamic CT and expiratory CT can show luminal narrowing with expiration (14). TBM can also be diagnosed with bronchoscopy (Fig 7). TBM is treated with airway clearance, noninvasive ventilation, and stent placement in severe cases (14).

Posttransplant Lymphoproliferative Disease

Posttransplant lymphoproliferative disease (PTLD) after lung transplantation is a neoplastic process involving transformation

Table 1 (*continued*): Surgical, Medical, and Immunologic Complications of Lung Transplantation

Complication	Timing Following Surgery	Imaging Feature	Reference
Chronic	Months to years		
BOS		Air trapping at expiratory thin-section CT	(82,85)
RAS		Acute phase: lower lobe–predominant ground-glass and consolidative opacities Subacute and chronic phase: upper lobe–predominant fibrosis	(76,87)
ARAD		Air trapping at expiratory thin-section CT Centrilobular nodules	(76,87)
AFOP		Ground-glass opacities and consolidation Lobar and bronchovascular distribution No reversed halo sign	(92)

Note.—ACR = acute cellular rejection, AFOP = acute fibrinous and organizing pneumonia, AMR = antibody-mediated rejection, ARAD = azithromycin-responsive allograft dysfunction, BOS = bronchiolitis obliterans syndrome, HLA = antihuman leukocyte antigen, PTLD = posttransplant lymphoproliferative disease, RAS = restrictive allograft syndrome.

Table 2: Risk Factors of Primary Graft Dysfunction

Donor Related	Recipient Related	Surgery Related
Advanced age	Elevated pulmonary arterial pressures	Prolonged ischemic time
Prolonged mechanical ventilation	Idiopathic pulmonary fibrosis	Single lung transplant
Aspiration pneumonitis	Female sex	High potassium extracellular preservation solution*
Ventilator-associated pneumonia	BMI > 25 kg/m^2	Blood transfusions
Hemodynamic instability	Heart disease	Cardiopulmonary bypass

Note.—BMI = body mass index.
*More prone to cause vasoconstriction of allograft vasculature compared with intracellular and low-potassium solutions.

of B cells. In most cases, this process is mediated by replication of Epstein-Barr virus. Risk factors for PTLD are Epstein-Barr virus seronegative status prior to transplantation and immunosuppression. PTLD may occur as early as 1 month after transplantation in recipients who are Epstein-Barr virus seronegative (46). Late manifestations are more common and are associated with increasing degree of immunosuppression rather than Epstein-Barr virus serologic status (46).

Incidence rates of 1%–2% and mortality rates of 30%–60% due to PTLD have been cited in the literature (46,47). PTLD can develop any time after lung transplantation but is more likely to occur within the 1st year (46). Typically, in patients where PTLD develops within the 1st year after transplantation, intrathoracic and allograft involvement are common, involving 85% and 64% of patients, respectively (48). In a study by Paranjothi et al, late manifestations were more likely to have extrathoracic involvement, and only 12% had intrathoracic involvement (48).

The most common intrathoracic findings in patients with PTLD are solitary intraparenchymal mass (observed in up to 50% of patients) and solitary or multiple pulmonary nodules (observed in 40%–50% of patients) (46,49). Usually, masses and nodules have homogeneous attenuation. Less commonly, a hazy halo or central necrosis can be observed (halo sign), similar to pulmonary aspergillosis (49). These masses and nodules exhibit fluorodeoxyglucose avidity with PET/CT imaging (Fig 8). Other findings include intrathoracic lymphadenopathy and airspace consolidation, both of which have been reported in 7%–10% of patients (49). Other less common manifestations of PTLD include pleural effusion, pericardial effusion, and chest wall soft-tissue nodules and masses (49). The second most common site of PTLD involvement in lung transplant recipients is the gastrointestinal tract, affecting up to 20% of patients with PTLD (46). Early recognition can alter management and affect prognosis. Reduction of immunosuppression is the initial treatment of PTLD (46). Rituximab alone or combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (a combination called *R*-CHOP) are used for more extensive disease (46). Imaging can be used to monitor treatment response.

Primary Disease Recurrence

Disease recurrence after lung transplantation may occur at any time, but occurs most commonly in the late postoperative period, months to years after lung transplantation (50). With a recurrence rate of 35%, sarcoidosis is the most com-

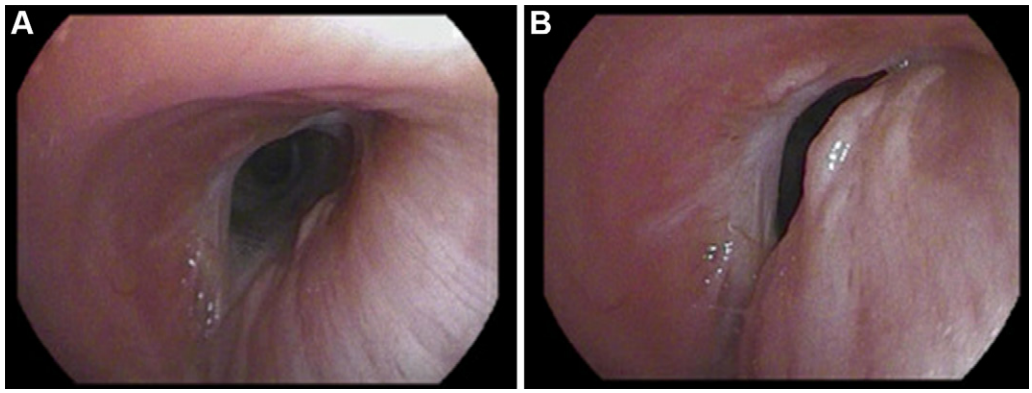

Figure 7: Images in a 65-year-old woman with tracheobronchomalacia after right lung transplantation for interstitial lung disease. Bronchoscopic images show **(A)** a normal caliber right mainstem bronchus during inspiration and **(B)** a collapsed and narrowed right mainstem bronchus during expiration. These findings are compatible with bronchomalacia.

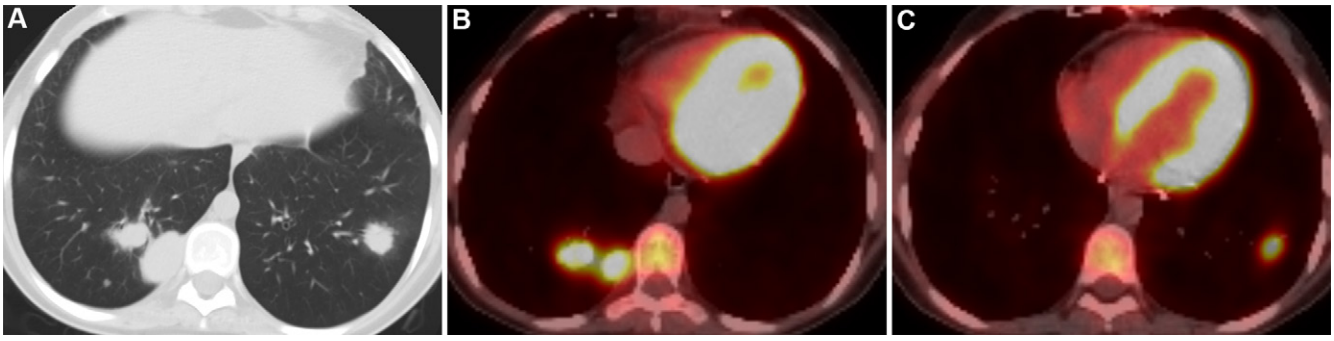

Figure 8: Images in a 24-year-old man with posttransplant lymphoproliferative disease identified 18 months after bilateral lung transplantation for cystic fibrosis. **(A)** Axial chest CT and **(B, C)** axial fluorodeoxyglucose PET/CT images show spiculated bilateral pulmonary nodules with intense fluorodeoxyglucose avidity.

mon recurrent disease in lung transplant recipients (50). In most cases, recurrent sarcoidosis is an incidental finding diagnosed with transbronchial biopsy and without associated imaging features. When imaging features are present, solitary nodule and miliary nodules are the most common findings (50).

Other reported biopsy-proven recurrent diseases include lymphangioleiomyomatosis (Fig 9), Langerhans cell histiocytosis, pulmonary alveolar proteinosis (Fig 10), and diffuse panbronchiolitis (50). Although recurrent disease manifests with similar symptoms, signs, and imaging as the original disease, there are no definitive guidelines for the treatment approach, and management varies on case-by-case basis.

Lung Cancer

The risk of lung cancer in lung transplant recipients increases with smoking exposure, immunosuppression, increasing age, and longer survival after transplantation (51,52). Additionally, immunosuppression can contribute to rapid spread of disease. In patients who have undergone single-lung transplantation, lung cancer most commonly occurs in the native lung (51). Risk factors associated with native lung cancer include underlying lung damage such as emphysema and idiopathic pulmonary fibrosis, native right lung, older age, and smoking history (53). The reported native lung cancer incidence rate is significantly higher in patients with idiopathic pulmonary fibrosis than patients with chronic obstructive pulmonary disease, with an incidence rate ratio of 1.6 and 1.1, respectively (53). Lung cancer can also originate from donor lungs (Fig 11).

It is essential to consider the possibility of lung cancer in enlarging opacities seen at routine CT and compare findings with multiple prior radiographs and CT scans to reduce a delay in diagnosis (55). Additionally, cancerous masses often exhibit fluorodeoxyglucose avidity, and CT or PET/CT can be considered in patients where lung cancer is clinically suspected (55). When CT or PET/CT scans exhibit findings suspicious for cancer, a definitive tissue biopsy diagnosis can be performed. While lung cancer treatment guidelines for patients without lung transplantation can serve as a foundation, the optimal treatment regimen warrants a multidisciplinary discussion that takes into consideration the individual needs of transplant recipients. Medical complications and their imaging findings are summarized in Table 1.

Immunologic Complications

Hyperacute Rejection

Hyperacute rejection is a complication that occurs following lung transplantation in recipients who have preformed antihuman leukocyte antigen (HLA) antibodies and is extremely rare due to improvement in HLA antibody screening and crossmatch techniques (56). To our knowledge, only case reports are cited in the literature (57–60).

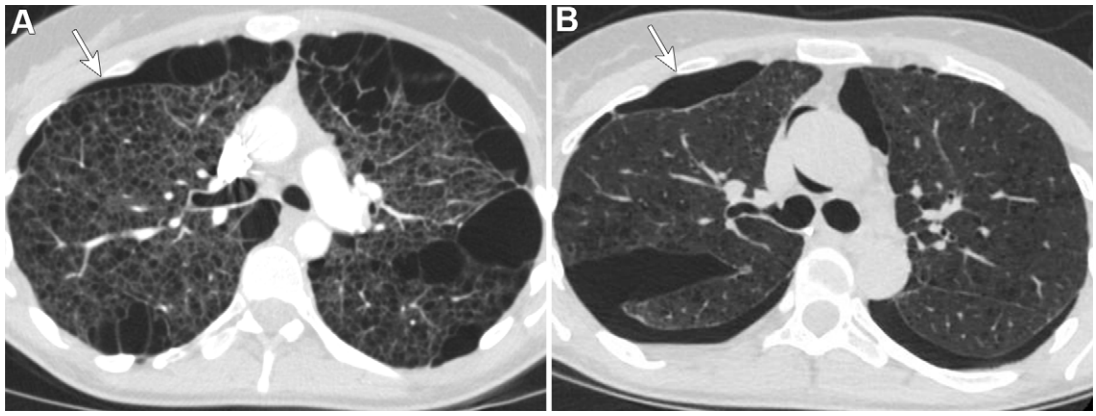

Figure 9: Images in a 32-year-old woman with lymphangioleiomyomatosis recurrence. **(A)** Axial CT image shows multiple small thin-walled cysts and larger subpleural bulla in a pretransplant patient with lymphangioleiomyomatosis. There is a small right pneumothorax (arrow). **(B)** Axial CT image obtained 7 years after bilateral lung transplantation shows multiple small bilateral thin-walled cysts and trace right pneumothorax (arrow) compatible with lymphangioleiomyomatosis recurrence. There is also small pneumomediastinum.

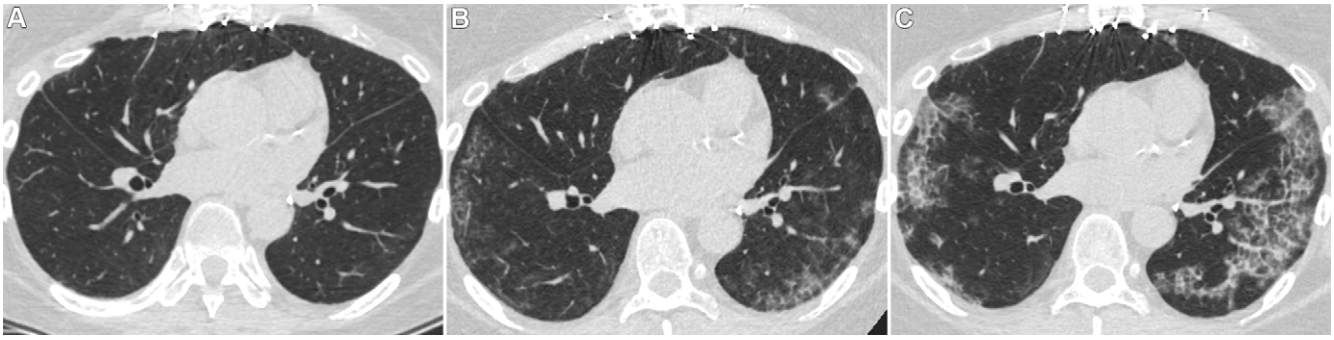

Figure 10: Images in a 55-year-old woman with pulmonary alveolar proteinosis recurrence. Axial CT lung window images at **(A)** 2 months, **(B)** 1 year, and **(C)** 2 years after lung transplantation show increasing patchy ground-glass opacities and septal thickening (crazy paving) compatible with recurrence of pulmonary alveolar proteinosis.

Signs of hyperacute rejection are usually observed intraoperatively. Within minutes to hours of vascular anastomosis, the transplanted lung becomes grossly edematous, mottled, and cyanotic (57). Chest radiography shows diffuse consolidative opacities, and CT shows ground-glass opacities and consolidations (59,60). There is no definitive treatment for hyperacute rejection, and it results in failure of the transplanted allograft.

Acute Allograft Rejection

Acute allograft rejection can occur any time over the life of a lung allograft but occurs most commonly weeks to months following surgery and affects one in four lung transplants (61). Acute allograft rejection has been identified as a major risk factor for chronic rejection and graft failure (62). Typically, 1%–4% of transplant recipient deaths within 1 year of transplantation have been attributed to acute allograft rejection (61). The two types of acute allograft rejection are acute cellular rejection (ACR) and antibody-mediated rejection (AMR). Both types are associated with increased risk of CLAD (63).

ACR is the more widely recognized form of acute allograft rejection, affecting up to 25% of lung transplant recipients (64). It is a lymphocyte-predominant inflammatory response affecting allograft blood vessels and airways. It is a result of T lymphocytes recognizing foreign HLAs (65). Symptoms of ACR include dyspnea, fever, and leukocytosis (66). CT findings associated with ACR include ground-glass and consolidative opacities in peribronchovascular distribution, pleural effusion, pleural thickening, and volume loss (67) (Figs 12 and E1 [supplement]). In isolation, either of these findings are neither sensitive nor specific. However, in a study by Gotway et al, the combination of volume loss and pleural thickening was only observed in patients with histopathologically proven ACR (67).

Transbronchial biopsy is the standard diagnostic test for ACR and can be used to grade severity. Mononuclear cell infiltration around small vessels and/or small airways is the histopathologic hallmark of ACR (68). The treatment of ACR depends on histologic and clinical severity. Most transplant centers treat mild ACR with high-dose steroids. High-grade and recurrent ACR can be treated with antithymocyte globulin or alemtuzumab, a CD52 antibody (68). In these cases, management includes monitoring blood counts and assessing symptoms of serum sickness. Functional and radiographic improvement is common with optimal management.

AMR is a more recently recognized entity, and incidence rates remain under investigation (69). It is mediated by B cells and is a result of circulating or de novo recipient antibodies acting against the allograft HLA antigens (68). It is more difficult to diagnose compared with ACR due to lack of symptoms and lack of specific pathologic features. However, it can progress rapidly and is associated with mortality rates of up to 47% (69). The

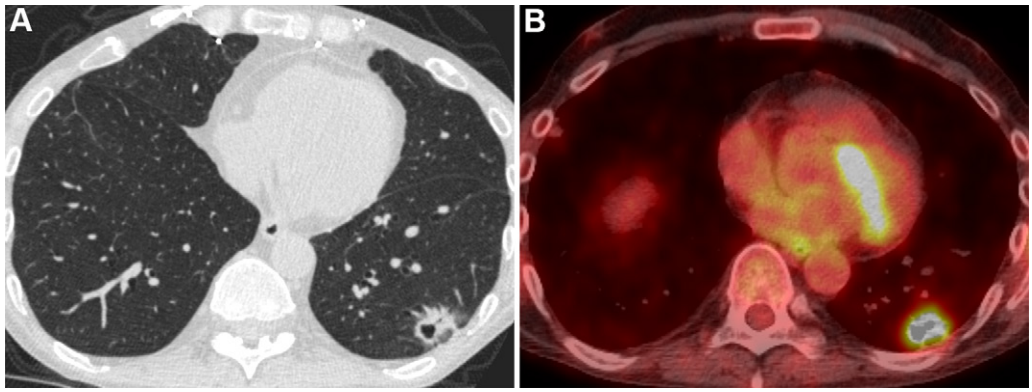

Figure 11: Images in a 57-year-old man with adenocarcinoma of the lung allograft 16 years after bilateral lung transplantation for idiopathic pulmonary fibrosis. **(A)** Axial CT image shows a left lower lobe spiculated nodule with central cavitation, and **(B)** axial fluorodeoxyglucose PET/CT image shows intense fluorodeoxyglucose uptake of the nodule. Biopsy proved primary adenocarcinoma of the lung.

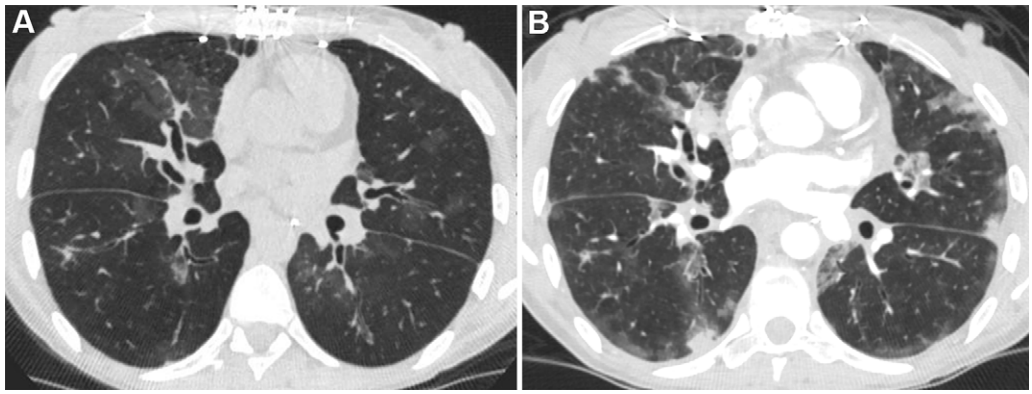

Figure 12: Images in a 35-year-old man with acute cellular rejection after bilateral lung transplantation for cystic fibrosis. **(A)** Axial chest CT lung window image 2 years and 7 months after transplantation shows bilateral ground-glass opacities. **(B)** Axial chest CT lung window image 2 years and 8 months after transplantation shows increased mixed-attenuation nodular opacities.

most common CT features of AMR are ground-glass opacities and air trapping (70). Air trapping is characterized by geographic areas of decreased attenuation of lung parenchyma that become more pronounced on expiratory CT images. Pleural effusions and consolidation have also been reported (70) (Fig E2 [supplement]). Antibody titers are helpful in diagnosis of AMR (71). The treatment of AMR is directed toward depletion of antibodies by plasmapheresis in the acute phase and subsequent inhibition of antibody-producing plasma cells and B cells (71). Anti-CD20 antibodies (such as rituximab) inhibit B cells, and proteasome inhibitors (such as carfilzomib and bortezomib) inhibit plasma cells (70,71). Intravenous immunoglobulin infusions can be administered periodically (70,71). In both ACR and AMR, close clinical follow-up, repeat biopsies, and monitoring of pulmonary function are essential to assess treatment response and guide management.

Chronic Lung Allograft Dysfunction

Despite advances in immunosuppression, the median 5-year and 10-year survival rates of lung transplant recipients are 54% and 32%, respectively (61). CLAD is the most common chronic complication of lung transplantation and the most clinically significant limiting factor of long-term survival (62). CLAD is an overarching term for a heterogeneous group of pathologic conditions that result from chronic allograft rejection in the setting of autoimmune response, inflammation, and dysregulated repair (72). Risk factors for developing CLAD include PGD, ACR, AMR, infections, gastroesophageal reflux, and noncompliance with immunosuppression (73).

In the literature over the past 7 years, the two most widely recognized phenotypes of CLAD are bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). BOS and RAS are not mutually exclusive. Among patients who develop CLAD, the incidence of BOS is 65%–75%, and the incidence of RAS is approximately 35% (74). There is a disparity in prognosis between these processes, with the average median survival at the time of diagnosis of BOS and RAS being 3–5 years and 6–18 months, respectively (74). Other less recognized entities that have been associated with BOS and RAS, and have been considered to be separate forms of CLAD by some sources, are azithromycin-responsive allograft dysfunction (ARAD) and acute fibrinous and organizing pneumonia (AFOP) (74–76). Their incidence is not yet established.

BOS is the most common form of CLAD. In BOS, chronic autoimmune response leads to abnormal regeneration and

Table 3: Bacterial, Viral, and Fungal Infections after Lung Transplantation

Type	Timing Following Surgery	Organism	Helpful Imaging Feature	Reference
Nonmycobacterial bacterial infection				
Hospital-acquired	Days to weeks	Methicillin-resistant *Staphylococcus aureus*	Tree-in-bud opacities and centrilobular nodules (bronchopneumonia)	(98,101,102,105)
		Pseudomonas aeruginosa	Cavitation	(98,101,102,105)
		Klebsiella pneumoniae	Lobar consolidation	(101,102)
			Bulging fissure	
			Cavitation	
Typical community-acquired	Anytime	*Streptococcus pneumoniae*	Lobar consolidation	(101)
		Haemophilus influenzae	Tree-in-bud opacities and centrilobular nodules (bronchopneumonia)	(98,101,105)
		Staphylococcus aureus	Tree-in-bud opacities and centrilobular nodules (bronchopneumonia)	(98,101,102,105)
			Cavitation	
Atypical community-acquired	Anytime	*Legionella*	Interlobular and peribronchial thickening	(101)
		Mycoplasma pneumoniae		(98,101,105)
		Chlamydia pneumoniae	Tree-in-bud opacities and centrilobular nodules (bronchopneumonia)	(98,101,105)
Other opportunistic	Weeks to months	*Nocardia*	Nodules and masses	(101,102,104)
			Cavitation	
		Pseudomonas aeruginosa	Tree-in-bud opacities and centrilobular nodules (bronchopneumonia)	(98,101,105)
			Cavitation	
		Burkholderia	Multilobar consolidation	(103)
			Cavitation	
Mycobacterial infections				
Nontuberculous	Months	*Mycobacterium avium* complex	Classic upper lobe–predominant consolidation and cavitation	(105,112)
		Mycobacterium abscessus complex	Nonclassic right middle lobe and lingular-predominant tree-in-bud opacities and centrilobular nodules (bronchopneumonia)	
		Mycobacterium kansasii		
Tuberculous	Months	*Mycobacterium tuberculosis*	Primary lymphadenopathy, consolidation, pleural effusion	(107,110)
			Postprimary upper lobe–predominant consolidation, cavitation, centrilobular nodules	
			Miliary-disseminated tiny nodules	
Viral infection				
Nonopportunistic	Anytime	Picornaviridae	Ground-glass opacities	(116)
		Adenoviridiae	Bronchial wall thickening	
		Orthomyxoviridae	Interlobular septal thickening	
		Coronaviridae		
		Paramyxoviridae		

Table 3 (*continues*)

fibroproliferation of the small airways (77). Patients with BOS present with progressive dyspnea. Clinically, the diagnosis of BOS is defined by chronic, progressive, and irreversible obstructive pulmonary function. More specifically, this has been defined as a 20% drop in forced expiratory volume in 1 second (FEV_1) from baseline at two time points 3 weeks apart without an identifiable cause (78). While BOS describes the clinical syndrome, obliterative bronchiolitis (OB) is the anatomic process associated with BOS. The hallmark of OB is fibrotic scarring causing narrowing and/or obliteration of the terminal and respiratory bronchioles (73,79). Due to the patchy nature of OB, confirming the diagnosis histologically is difficult, and only

Table 3 (*continued*): Bacterial, Viral, and Fungal Infections after Lung Transplantation

Type	Timing Following Surgery	Organism	Helpful Imaging Feature	Reference
Opportunistic Herpesviridiae	Weeks to months	Cytomegalovirus	Ground-glass opacities Diffuse distribution	(117,118)
		Herpes simplex virus	Pleural effusion Multifocal distribution	(117,118)
		Varicella-zoster virus	Nodules with halo sign Tiny ill-defined nodules Multifocal distribution	(117,118)
Fungal infections				
	Weeks to months	*Aspergillus*	Semi-invasive nodular consolidation, cavitation Bronchoinvasive tree-in-bud opacities and centrilobular nodules Angioinvasive nodules with halo sign	(120)
		Candida	Multiple nodules and areas of consolidation Miliary pattern	(120)
		Rhizopus or *Mucor*	Reversed halo sign	(120)
		Pneumocystis jirovecii	Ground-glass opacities Upper lobe predominant Peripheral sparing	(101)

15%–48% of patients can be diagnosed from bronchial biopsies, due to low yields (73). Therefore, recognizing OB features at imaging adds value in management and treatment of these patients.

The hallmark of BOS at thin-section CT is air trapping. Air trapping can be seen in the early phases of BOS even without other CT manifestations such as bronchiectasis (80) (Fig E3 [supplement]). A sensitivity of 83% and specificity of 89% for air trapping in the context of BOS have been reported (81). The high sensitivity and specificity underline the importance of thin-section CT in patients who have undergone lung transplantation. CT techniques that have been associated with improved detection of BOS include thin sections, spirometrically gated CT, and prone imaging (82). Spirometrical gating is useful to identify air trapping on expiratory imaging. Thin-section imaging improves detection of small centrilobular nodules expected to be seen in BOS. Prone imaging is useful for minimizing dependent atelectasis. In our experience, this can help better detection of centrilobular nodules when there is substantial atelectasis. Minimizing atelectasis with prone imaging can also help with better detection of mild air trapping by providing a better assessment of lung parenchyma at inspiratory imaging for better comparison with expiratory phase imaging (80). Other findings associated with BOS include bronchial wall thickening and bronchiectasis (83).

RAS is a more recently recognized form of CLAD. The pathophysiologic mechanisms of RAS are currently under investigation, but features reported in the literature include collagen deposition, pleuroparenchymal fibroelastosis, and diffuse alveolar damage (84). Clinically, the hallmark of RAS is a restrictive pattern of pulmonary function decline (85). Sato et al have proposed clinical diagnostic criteria of FEV_1 of less than 80% and total lung capacity of less than 90% of baseline (85). Histologic findings of RAS include damaged alveoli and extensive fibrosis in the alveolar interstitium, visceral pleura, and interlobular septa (85). Imaging plays an important role in the diagnosis of RAS given the unreliable yield of transbronchial biopsy. CT findings associated with RAS are upper lobe–predominant fibrosis, traction bronchiectasis, architectural distortion, volume loss, peripheral consolidation, and subpleural thickening (Fig E4 [supplement]) (74,85). A stepwise progression pattern of RAS has been described in the literature, with ground-glass opacities and lower lung–predominant consolidation observed in acute exacerbations of RAS and progressive apical-predominant fibrosis observed in the subacute and chronic stages of the disease (78,86). Additionally, there are data to suggest that some radiographic findings can precede the clinical presentation of RAS, thus adding value to early recognition of imaging features associated with the disease (87).

Although BOS and RAS are the two most widely recognized forms of CLAD, this diagnosis encompasses a wide range of symptoms, imaging findings, prognosis, and histopathologic features. As a result, there exists an ongoing effort to classify this heterogeneous group of diseases. Other less widely recognized entities include ARAD, a more recently recognized form of CLAD, and AFOP, a process associated with BOS and RAD and occasionally considered a CLAD subtype (76,88).

ARAD, formerly known as *neutrophil reversible allograft dysfunction*, has been defined as an FEV_1 increase of 10% or greater after 2–3 months treatment with azithromycin (88). This treatment response distinguishes ARAD from other forms of CLAD.

Response to azithromycin had been previously thought to be related to the degree of neutrophilia in bronchoalveolar lavage. However, recent literature suggests that this association may have been overestimated, and the term *neutrophil reversible allograft dysfunction* has fallen out of favor (75,78). Although the mechanism of ARAD is not fully understood, inflammatory cytokine interleukin-8 is thought to be implicated in an inflammatory response (89). As a more recently recognized form of CLAD separate from BOS and RAS, the incidence of ARAD is under investigation. Clinically, the diagnosis of ARAD is made retrospectively, upon seeing a response in FEV_1 with azithromycin treatment in patients thought to have BOS. Tomographic findings of ARAD are similar to BOS and improve or resolve after treatment with azithromycin (90). In a study by de Jong et al, patients with ARAD were more likely to have centrilobular (including tree-in-bud) opacities at CT compared with patients with BOS (90) (Fig E5 [supplement]).

AFOP is a pattern of lung injury that has been observed in lung transplant recipients. It is presumed that AFOP is a transient pathologic condition associated with BOS and RAS (91). However, some consider it a separate CLAD subtype (76). The frequency of AFOP has been cited at 1.7%–11%, and the prognosis is poor, with median survival of 101–367 days (76,91). AFOP is characterized by organizing intra-alveolar fibrin in the absence of hyaline membranes, eosinophils, granulomatous inflammation, and intrabronchial fibrosis (76). The absence of intrabronchial fibrosis distinguishes AFOP from organizing pneumonia, which is a form of lung injury that can also be observed in lung transplantation but is not considered a form of CLAD (76). Much like organizing pneumonia, the most common tomographic manifestations of AFOP are consolidations and ground-glass opacities (Fig E6 [supplement]) (92). The classic appearance of organizing pneumonia includes opacities with a rim of consolidation around a central ground-glass opacity (reversed halo sign) (Fig E7 [supplement]) (92). Although this appearance can help distinguish organizing pneumonia from AFOP, the reference standard for differentiating these entities is histopathologic findings. AFOP is bilateral in most cases and has been associated with subpleural and bronchovascular distributions (76,91,92).

Options for treatment of CLAD are limited. Azithromycin has shown some promise in the management of ARAD as described above and can be used for prophylaxis and early management of other types of CLAD (72). The use of alemtuzumab and extracorporeal photophoresis remain experimental and are of unclear benefit (93). Given the lack of definitive cure for CLAD, strategies for preventing and delaying this disease process are paramount. These include optimization of immunosuppression and medication compliance and mitigation of risk factors including gastrointestinal reflux disease, recurrent infections, and aspiration (72). Immunologic complications and their imaging findings are summarized in Table 1.

Infectious Complications

Infection is the leading cause of mortality in the intermediate postoperative period. Infections account for 37% of deaths between 30 days and 1 year following transplantation, but they can occur at any time following surgery (1). The most common types of infection are respiratory and catheter-related infections (1). Lung transplant recipients are at high risk for infections due to immunocompromised status, impaired pulmonary clearance mechanisms after denervation, and impaired lymphatic drainage (94). Other factors contributing to the increased risk of infection include aspiration, colonization, and contact of allograft with the atmosphere (95). These factors predispose transplant recipients to both community-acquired and hospital-acquired infections, as well as infections by opportunistic infectious species, including fungal organisms. An overview of infections and their imaging manifestations are described in Table 3.

Nonmycobacterial Bacterial Infections

Bacterial infections account for most infections in the intermediate postoperative period (30 days to 1 year) (96). In the early postoperative period (30 days following transplantation), the most common causes of pneumonia are hospital-acquired infections such as methicillin-resistant *Staphylococcus aureus* and gram-negative bacilli such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (97). In addition to hospital-acquired infections, transplant recipients are at risk for infection with both typical and atypical community-acquired species at any time. The most common bacterial species are *Streptococcus pneumoniae, Haemophilus influenzae,* and *S aureus*, and atypical species include *Legionella* spp, *Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae* (98,99). Transplant recipients are also at the highest risk for opportunistic bacterial infections weeks to months after surgery, but these can occur at any time (24). Common species include *P aeruginosa, Burkholderia,* and *Nocardia* (98). Tuberculous and nontuberculous mycobacteria also fall under the category of opportunistic disease and will be discussed separately.

Most bacterial infections manifest with clinical symptoms and signs of pneumonia. In terms of tomographic findings, CT alone is not sufficient to identify the cause of the offending organism. However, there are features that are more specific to certain organisms. *S aureus, P aeruginosa, K pneumoniae*, *Burkholderia,* and *Nocardia* are more likely to have cavitating consolidative opacities (100,101). Nodules and masses are common presentations of *Nocardia* (102). *S pneumoniae* and *K pneumoniae* typically manifest as lobar consolidation (99). *K pneumoniae* is also associated with the bulging fissure sign, which represents displacement of fissures from mass effective and extensive lobar consolidation (100). *Burkholderia* is often multilobar (101). Organisms that are typically associated with a bronchopneumonia pattern of peribronchial nodules and tree-in-bud opacities include *S aureus, P aeruginosa, H influenzae, C pneumoniae*, and *M pneumoniae* (96,99,103). Interstitial findings are more specific to atypical community-acquired infections (*Legionella* spp*, C pneumoniae,* and *M pneumoniae*) and include bronchial wall thickening and interlobular septal thickening (99). Bacterial infections are managed with antibiotics and close clinical monitoring (98,101).

Mycobacterial Infections

Mycobacterial infections are uncommon and typically occur more than 4 months following lung transplantation (24).

Implicated organisms include tuberculous and nontuberculous species.

Infection with *Mycobacterium tuberculosis* in lung transplant recipients is rare in North America, with an incidence rate of less than 1%, but incidence of up to 15% has been described in endemic areas of the world (104). Variable incidences of nontuberculous infection in transplant recipients have been reported and range from 1% to 18% (105,106). Both tuberculous and nontuberculous infections have been associated with death in lung transplant recipients. Torre-Cisneros et al reported a mortality rate of 9.5% attributable to tuberculous infection, and Huang et al reported a statistically significant increased risk of death with a hazard ratio of 2.6 in patients with nontuberculous infections (106,107).

Clinically, patients present with nonspecific symptoms of infection. Serologic findings and cultures can be used to diagnose mycobacterial infection. Primary, postprimary, and miliary forms of tuberculous infections may be observed in transplant recipients (108). CT findings include lymphadenopathy, pulmonary consolidation, and pleural effusion for primary infection and upper lung–predominant consolidation, cavitation, and centrilobular nodules for postprimary infection (108). The hallmark of miliary tuberculosis is numerous tiny parenchymal nodules (108). The most common nontuberculous infections are *Mycobacterium avium* complex, *Mycobacterium abscessus* complex, and *Mycobacterium kansasii* (105,109). Imaging features of nontuberculous infections can follow a classic pattern or nonclassic pattern (110). The classic pattern resembles postprimary tuberculosis and is characterized by upper lung–predominant consolidation and cavitation (110). The nonclassic pattern is characterized by centrilobular nodules (including tree-in-bud nodules) and bronchiectasis predominantly in the right middle lobe and lingula (103).

The treatment for mycobacterial infections depends on the implicated organism. The first line agents for the treatment of mycobacterial tuberculosis are isoniazid, a rifamycin (usually rifampin), ethambutol, and pyrazinamide (104). *M avium* complex is treated with a three-drug regimen of a macrolide, a rifamycin, and ethambutol (106). For *M abscessus* complex, the current available treatments are clarithromycin, amikacin, and cefoxitin (109).

Viral Infections

Common community-acquired respiratory viral organisms include Picornaviridae (rhinovirus and enterovirus), Adenoviridiae (adenovirus), Orthomyxoviridae (influenza A and B), Coronaviridae (coronavirus), and Paramyxoviridae (respiratory syncytial virus, parainfluenza virus, and human metapneumovirus) (111).

With respect to opportunistic viral infections, the most common viruses belong to the Herpesviridiae family, which includes cytomegalovirus, herpes simplex virus, and varicella-zoster virus (98). The most common opportunistic viral infection in lung transplant recipients is cytomegalovirus (98). Cytomegalovirus infection affects 54%–92% of lung transplant recipients not receiving prophylaxis (112). The greatest risk factor for cytomegalovirus disease is a serological mismatch between the donor and the recipient (the recipient is cytomegalovirus seronegative and the donor is seropositive) (112). Cytomegalovirus infection has been associated with chronic rejection and graft loss and has also been cited as an independent risk factor for mortality with a statistically significant hazard ratio of 1.4 (113).

Viral infections manifest with shortness of breath, fever, malaise, and leukocytosis. CT scans can still appear normal when a patient has a viral pneumonia. When compared with bacterial infections, viral infections are less likely to follow a lobar distribution or manifest with airspace consolidation (114). Ground-glass opacities, bronchial wall thickening, and interlobular septal thickening are more common features (114). Features more specific to varicella-zoster virus are the halo sign and 5–10-mm ill-defined nodules that may be confluent (115,116). Pleural effusions are most common with herpes simplex virus (116). Ground-glass opacities are most common with cytomegalovirus but can also be seen with varicella-zoster virus and herpes simplex virus (116). Herpes simplex virus and varicella-zoster virus are more likely to present with multifocal distribution, whereas cytomegalovirus is usually diffuse (115). Correlation with symptoms and serologic results is essential for a definitive diagnosis. Management of viral infections includes supportive care, antivirals, and prophylaxis when appropriate (98).

Fungal Infections

Fungal infections typically occur months after transplants as immunosuppressant treatments take effect (24). Fungal infections have an estimated incidence of 15%–35% and mortality rate of up to 80% (117). Airway colonization, frequent viral and bacterial infections, and chronic rejection are risk factors associated with fungal infections (98).

Aspergillus is the most common fungal infection in lung transplant recipients, with an incidence of 32% (111). *Aspergillus* infection manifests with cough and dyspnea. Laboratory tests including galactomannan, polymerase chain reaction, and 1,3-β-D-glucan assay assist in the diagnosis (112). Immunocompromised hosts are at risk for semi-invasive, airway-invasive, and angioinvasive aspergillosis (118). At CT, semi-invasive aspergillosis manifests with upper lobe–predominant nodular airspace opacities with or without cavitation, airway-invasive aspergillosis manifests with centrilobular and tree-in-bud opacities (bronchopneumonia pattern), and angioinvasive aspergillosis manifests with the halo sign (Fig E8 [supplement]) (118). Other fungal species implicated in lung transplantation infections include *Pneumocystis jirovecii, Candida*, and *Rhizopus*. Features of *P jirovecii* pneumonia include upper lobe–predominant, periphery-sparing, ground-glass opacities (Fig E9 [supplement]) (99). *Candida* infection can manifest with multiple nodules and regions of consolidation or a miliary pattern (118). Reversed halo sign can be seen in *Mucor* infection (a *Rhyzopus* species) (Fig E10 [supplement]) (118). Fungal infections are treated with antifungals such as voriconazole and amphotericin, and trimethoprim and sulfamethoxazole in the case of *P jirovecii* pneumonia (98).

Conclusion

Considering the rapid increase in the number of lung transplantations in the past decade and the importance of imaging surveillance, it is important for radiologists to become familiar

with complications of lung transplantation and their expected imaging features.

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