Lung Allograft Dysfunction

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Disclaimer: We do not have any conflict of interest or financial gain to disclose
Lung Allograft Dysfunction

- Survival after lung transplantation (5 year survival ≈ 55%) remains shorter than survival after transplantation of other solid organs
- This has been mainly attributed to the development of chronic rejection
- Rejection is responsible for 30% mortality after lung transplantation
- Lung allograft dysfunction may be acute (ALAD) or chronic (CLAD), leading to decline in forced expiratory value in 1 second (FEV₁)
Acute Lung Allograft Dysfunction (ALAD)

• ALAD may be due to various conditions that affect the graft including infection, pulmonary embolism, acute rejection, etc.

• Acute rejection is characterized by presence of perivascular & interstitial mononuclear cell infiltrate.

• ALAD can result from primary graft dysfunction (PGD) which can result from ischemia-reperfusion injury, airway injury, aspiration, donor-ventilator injury, or cold ischemia.
Primary Graft Dysfunction (PGD)

- PGD after lung transplantation is a significant source of early morbidity and mortality (≈30% incidence)
- PGD is a form of acute lung injury occurring within 72 h of lung transplantation
- PGD is graded according to PaO₂/FiO (P/F)
- Imaging findings are consistent with allograft pulmonary edema (non-cardiogenic)
- PGD is likely end result of multiple deleterious mechanisms provoked by donor brain death, mechanical ventilation, procurement, storage, and ischemic-reperfusion injury

*Porteous MK et al. Curr Opin Organ Transplant 2015;20:506*
ALAD secondary to acute rejection. 59 year old male, 4th day after single left lung transplant. CT shows extensive ground-glass and air-space opacities and patchy consolidation in the bilateral lungs.
ALAD secondary to acute rejection. 44 year old male, 12 days after single right lung transplant for COPD. CT shows extensive ground-glass and air-space opacities with denser consolidation in the right lower lobe.
Chronic Lung Allograft Dysfunction (CLAD)

- CLAD is an umbrella term that embraces all forms of chronic lung dysfunction (≥ 3 weeks) after transplant.
- Initially chronic rejection was defined as pathological obliterative bronchiolitis (OB) for which the clinical equivalent of bronchiolitis obliterans syndrome (BOS) was proposed.
- The inflammatory reaction in the airway lumen results in polypoid intraluminal granulation tissue with subtotal or total obliteration of airway lumen.
Chronic Lung Allograft Dysfunction (CLAD)

• Currently two principal phenotypes of CLAD dysfunction are recognized: obstructive CLAD and restrictive CLAD

• Obstructive CLAD is the typical BOS, which from a histopathology standpoint is characterized by obliterative bronchiolitis

• Restrictive CLAD has been termed restrictive allograft syndrome (RAS), which from a histopathology standpoint is characterized by pleuroparenchymal fibroelastosis
Lung Allograft Dysfunction (LAD)

**Acute LAD (ALAD)**
- Acute rejection
- Acute infection
- Other causes

**Suspected CLAD**
- FEV1 and/or FVC ≤90% ≥3 weeks

- No specific cause
- Specific cause (persistent acute rejection, infection, anastomotic stricture etc)

**CLAD**
- FEV1 and/or FVC ≤80% ≥3 weeks

- Restrictive CLAD (RAS)
- Obstructive CLAD (BOS)

Verleden GM et al. J Heart Lung Transplant 2014;33:127
Change in terminology for chronic rejection following lung transplantation

Past
Chronic rejection

Current
Chronic rejection

Vos R et al. Curr Opin Organ Transpl 2015;20:483
Bronchiolitis Obliterans Syndrome (BOS)

• BOS is an irreversible form of airflow obstruction
• BOS is defined as a delayed form of allograft dysfunction with persistent decline in forced expiratory volume in 1 second (FEV1) not caused by other known and potentially reversible causes of post-transplant loss of lung function
• BOS is thought to be caused by inflammation, destruction and fibrosis of small airways in the lung that leads to obliterative bronchiolitis (OB)
• May also develop as a complication of allogenic hematopoietic stem cell transplantation and bone marrow transplantation.
BOS Microscopic features

• Obliterative bronchiolitis (OB) is the histologic hallmark and is characterized by patchy submucosal peribronchiolar fibrosis / cicatrization of respiratory bronchioles, resulting in occlusion of the noncartilaginous airway.

• The initial phase is lymphocytic infiltration of the submucosa (i.e. lymphocytic bronchitis/ bronchiolitis), followed by epithelial cell injury, ulceration and fibroblast proliferation.

• Polypoid intraluminal granulation tissue ends in airway obstruction.

• Advanced BO include partial to completely acellular fibrotic airway scarring and obliteration, accumulation of foamy macrophages and retain mucus.
Bronchiolitis Obliterans

A) Bronchiolitis obliterans is characterized by lumen obstruction with a fibro-inflammatory polyp (arrow). B) Mucous plugging: the airway lumen is obstructed by mucus exudates. Advanced BO include partial to completely acellular fibrotic airway scarring and obliteration, accumulation of foamy macrophages and retain mucus.

Natural history and prognosis

• BOS affects >50% of lung transplant recipients who survive beyond 5 years, and accounts for a significant proportion of lung allograft loss and recipient mortality.

• BOS is also the most common long-term non-infectious pulmonary complication of allogenic hematopoietic stem cell transplantation.

• The clinical course of BOS is highly variable with a median survival of 3 to 4 years after onset, with higher mortality in those who develop the syndrome within two years of transplantation.

• No effective treatment exits for BOS. Immunosuppression remains the mainstay of therapy but intensified pharmacological immunosuppression has little effect on established BOS.
BOS: CT imaging findings

- Routine chest radiographs are neither sensitive nor specific
- Air-trapping (44%-64% sensitivity; 80%-100% specificity) is the HRCT finding that correlates best with the presence of OB
- Mosaic pattern of lung attenuation (4%-36% sensitivity; 96%-100% specificity) and air-trapping with persistent lucency of regions of lung parenchyma, are better demonstrated during expiratory scans
- Bronchial wall thickening (≈40% sensitivity; 80%-96% specificity), predominantly affecting the lower lobes
- Bronchiectasis (25%-40% sensitivity; 80%-96% specificity) and centrilobular nodules, generally mild may also be present

BOS In a 53 y/o female status post BLT (x2) for pulmonary hypertension and bronchiectasis. CT reveals extensive areas of mosaic attenuation, bilaterally
Path proven obliterative bronchiolitis (OB) in a 41 year old female with history of bilateral lung transplant. CT demonstrates mosaic pattern of lung attenuation in the bilateral lungs
Obstructive CLAD (BOS) in a 66 year old male, status post right single lung transplant, with decline in pulmonary function test. Biopsy confirmed obliterative bronchiolitis. CT shows mosaic pattern of lung attenuation.
Obstructive CLAD in a 56 year old female status post single right lung transplant for emphysema. CT shows bronchial dilation, scarring, and mosaic pattern of lung attenuation.
Chronic rejection in a 57 year old female with pulmonary fibrosis, status post left lung transplant. HRCT shows mosaic pattern of lung attenuation with patchy areas of diminished vascularity. Pulmonary function test and imaging findings were consistent with obstructive CLAD / BOS.
Restrictive Allograft Syndrome (RAS)

- Some lung transplant recipients develop a restrictive form of allograft dysfunction
- This has been termed restrictive allograft syndrome (RAS) and more recently restrictive CLAD
- RAS is characterized by restrictive pulmonary function decline with decreased forced vital capacity (FVC) and total lung capacity (TLC) in addition to decline in FEV1
- Pleuroparenchymal fibroelastosis is the major histopathologic correlate of RAS, with predominant subpleural distribution predominant in the upper lung zone
- Concurrent features of BO are also commonly present

Ofek E et al. Modern Pathology 2013;26:350
Restrictive Allograft Syndrome (RAS)

- Pleuroparenchymal fibroelastosis (100%) and interstitial fibrosis (>90%) predominantly in a biapical subpleural distribution are seen in nearly all patients with RAS.
- Concomitant presence of OB is also very common (87%), as well as diffuse alveolar damage (>80%) with organized pneumonia.
- On CT, RAS manifest as increased reticulation and pleural thickening more significantly in the mid and upper lung zones.
- Traction bronchiectasis are also common.

Ofek E et al. Modern Pathology 2013;26:350
Restrictive allograft syndrome in a 73 years old male s/p single left lung transplant for IPF, and worsening pulmonary function test. Chest radiographs show progressive reduction in allograft (left) lung volume (arrows) with increase interstitial markings. Fibrotic changes in the right lung are also noted.
CTs in the same patient. Comparison between exams less than two years apart show progressive scarring and pleural thickening in the left lung (arrows), with no significant interval change in the fibrotic native right lung.
CTs in the same patient, coronal reconstruction. Comparison between exams less than two years apart show progressive scarring and pleural thickening in the left lung (arrows), with no significant interval change in the fibrotic native right lung.
CTs in the same patient. Sagittal reconstruction through the left lung. Comparison between exams less than two years apart show progressive scarring and pleural thickening in the left lung (arrows), with no significant interval change in the fibrotic native right lung.
RAS in a 44 y/o male with pulmonary emphysema, status post single right lung transplant. Plain film and CT shows diminished right lung volume, multifocal scarring and right side pleural thickening.
35 y/o F with IPF, status post bilateral lung transplant. A. Chest radiograph in the early postoperative stage demonstrates normal healthy bilateral lungs. B. Chest radiographs 3 years later show biapical and subpleural fibrosis and diffuse interstitial coarsening with diminished lung volume, consistent with progressive restriction.
CT in the same patient. Axial images show progressive scarring and fibrosis, with pleural thickening bilaterally. Patient underwent new bilateral lung transplantation. The explanted lungs demonstrated pleuroparenchymal fibroelastosis.
Restrictive CLAD in a 69 y/o male patient status post BLT (3 times) with history of chronic rejection. CT shows reticular and ground-glass opacities with patchy peribronchovascular consolidation and pleural thickening (arrows)
Restrictive CLAD in a 50 y/o male s/p bilateral lung transplant. Radiographs and CT 2 years (A, B) and 4 years (C, D) after surgery shows progressive restrictive changes in the right lung, with volume loss and traction bronchiectasis.
Lung Allograft Dysfunction

- Lung allograft dysfunction following lung transplantation is a heterogeneous condition that includes acute and chronic allograft dysfunction.
- ALAD may be due to various conditions that affect the graft including infection, pulmonary embolism, acute rejection, etc.
- ALAD can also result from primary graft dysfunction (PGD) which can result from ischemia-reperfusion injury, airway injury, aspiration, donor-ventilator injury or cold ischemia.
- Currently, two principal phenotypes of Chronic Lung Allograft Dysfunction (CLAD) are recognized: obstructive CLAD and restrictive CLAD.
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Thank You