Common (obstructive) and atypical (restrictive) lung manifestations in cGVHD

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GvHD
Graft-versus-Host Disease
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Leibniz-Institut
für Immuntherapie
immune cells for life

Conflict of Interest

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- The talk describes off-label therapies for the treatment of GvHD

Pulmonary Manifestations of chronic GVHD

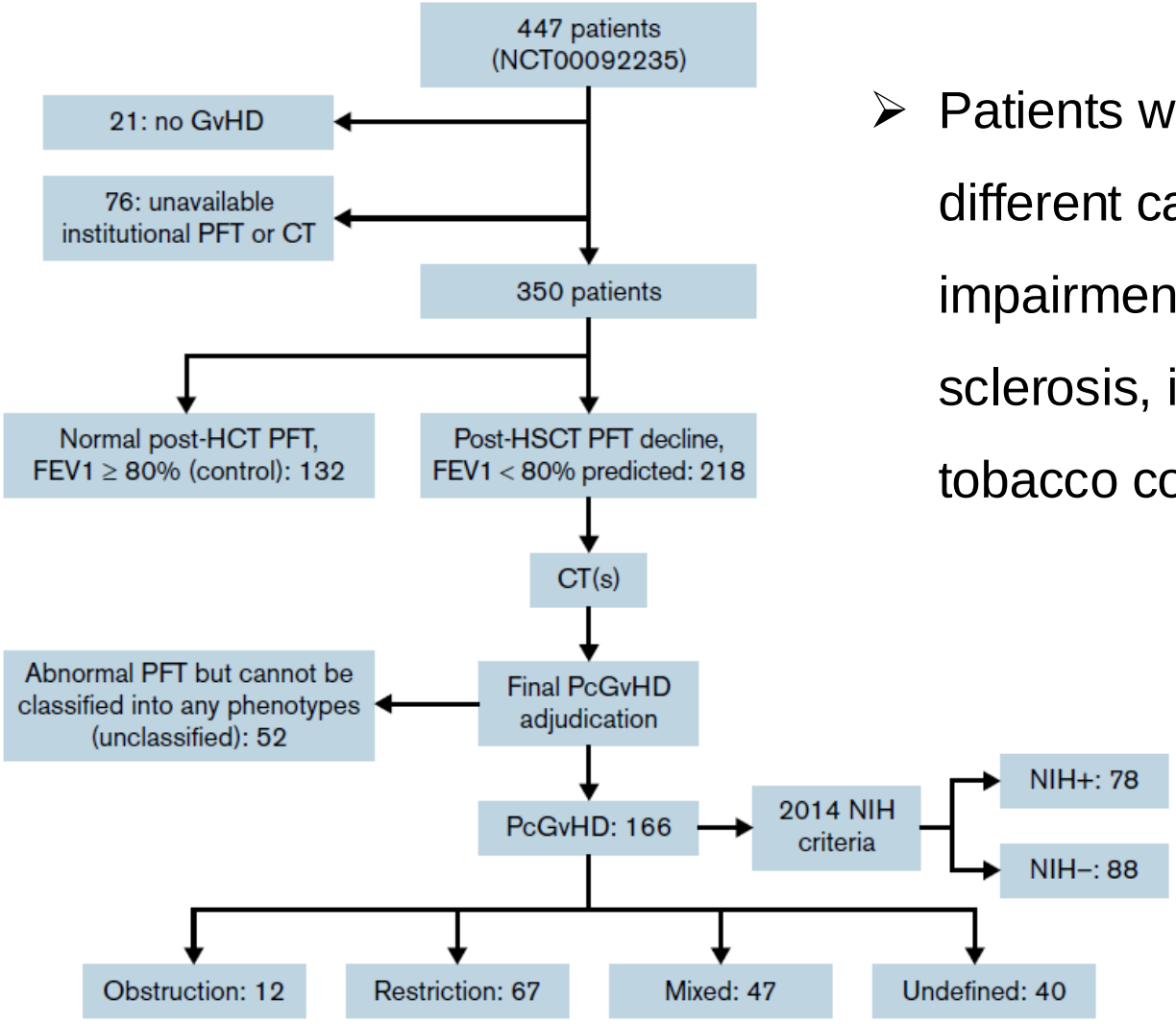
- Pulmonary manifestations of cGVHD can present with obstructive, restrictive and mixed pattern with a FEV < 80% (Wolff 2021, Pang 2022, Cuvelier 2022)

Criteria	NIH criteria	ISHLT CLAD criteria	Adapted criteria
Diagnosis	FEV1/VC < 0.7 or the 5th percentile predicted based on population-based reference; VC is either FVC or SVC, whichever is greater; FEV1 < 75% predicted with ≥ 10% decrease over less than 2 y, not corrected with albuterol	Persistent decline (> 3 mo, ≥ 20%) of FEV1 from the reference baseline; baseline is the mean of the best 2 post-transplant FEV1 measurements taken 3 wk apart	Abnormal pulmonary function after transplant (FEV1 < 80% predicted based on population-based reference), able to be classified into 1 of the 4 CLAD-PcGVHD subtypes, rule out other causes of pulmonary dysfunction
Phenotype	BOS: FEV1/VC < 0.7 or the 5th percentile predicted based on population-based reference; VC is either FVC or SVC, whichever is greater; evidence of air-trapping by expiratory CT or airway thickening or bronchiectasis by high-resolution CT, or air-trapping by PFT	BOS: obstruction (FEV1/FVC < 0.7), without restriction or CT opacity; RAS: restriction (TLC < 90% baseline) + CT opacity, FEV1/FVC ≥ 0.7; mixed: FEV1/FVC < 0.7, TLC < 90% baseline, with CT opacity; undefined: A. FEV1/FVC < 0.7, TLC < 90% baseline, NO CT opacity; B. FEV1/FVC < 0.7, TLC ≥ 90% baseline, WITH CT opacity	Obstruction: obstruction (FEV1/FVC < 0.7), without restrictive findings on PFT or CT; restriction: restriction (TLC < 90% predicted), with restrictive CT findings,* FEV1/FVC ≥ 0.7; mixed: FEV1/FVC < 0.7, TLC < 90% predicted, restrictive CT findings; undefined: A. FEV1/FVC < 0.7, TLC < 90% predicted, NO restrictive CT findings; B. FEV1/FVC < 0.7, TLC ≥ 90% predicted, WITH restrictive CT findings

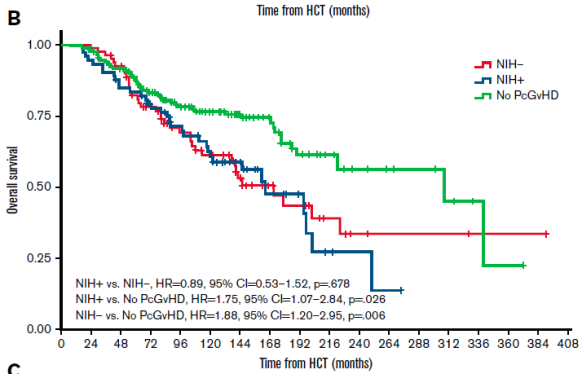
Pang 2022

- BOS: FEV1/VC < 0.7, no restrictive findings in PFT and CT
- Restrictive forms (organizing pneumonia, NSIP): FEV1/VC > 0.7, TLC < 90%, restrictive findings in PFT & CT

Pulmonary Manifestations of chronic GVHD



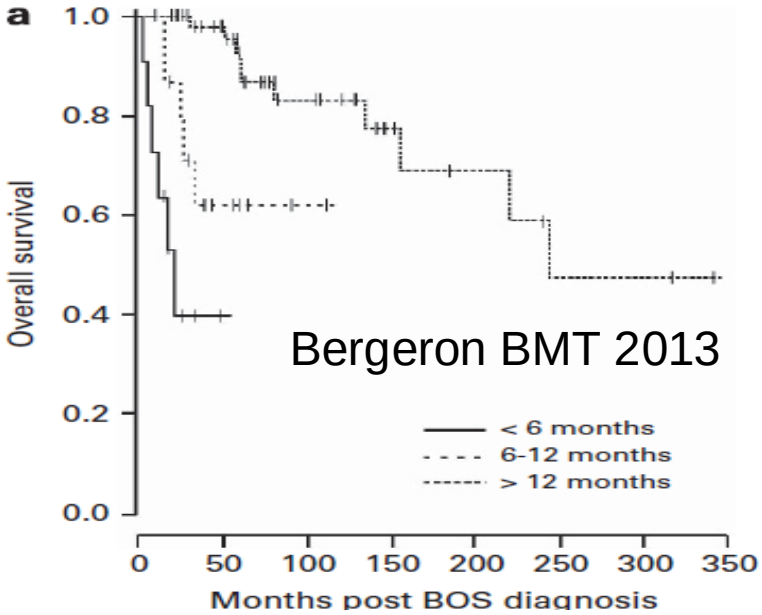
- Patients with cGVHD can have different causes of pulmonary impairment including chest wall sclerosis, impairment caused by tobacco consume

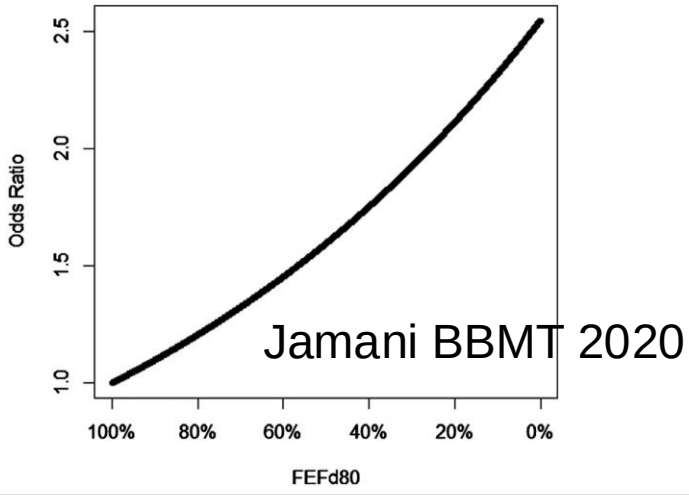


Pang 2022

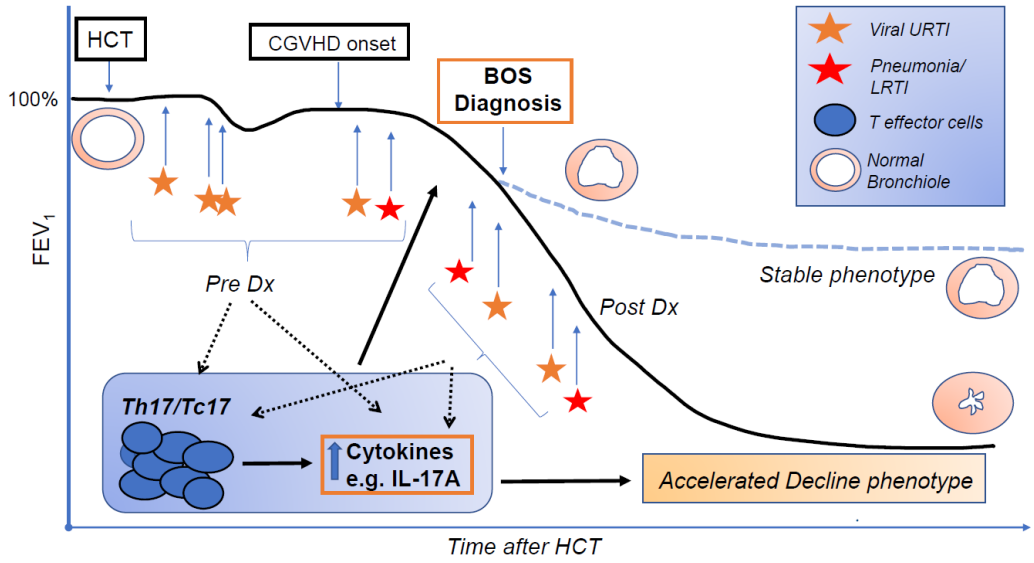
Bronchiolitis obliterans syndrome (BOS)

- occurs with an incidence of ~5% of all transplanted patients (10-15% of cGVHD patients)
- Early onset is associated with dismal prognosis (Bergeron 2013)
- Day 80/90 PFT is predictive (Jamani 2020)
- Risk factors are impaired lung function before Tx, nicotine abuse after Tx, cGVHD, viral airway infections (Sheshadri 2919, Erard 2006), chest irradiation
- manifest BOS is hardly reversable





Biology of BOS



(Chen 2016)

- sBAFF and CD21^{low} B cells are significantly higher in BOS patients compared to other cGVHD manifestations indicating a role of B cells supported by mice (Kuzmina 2013, Flynn 2014)

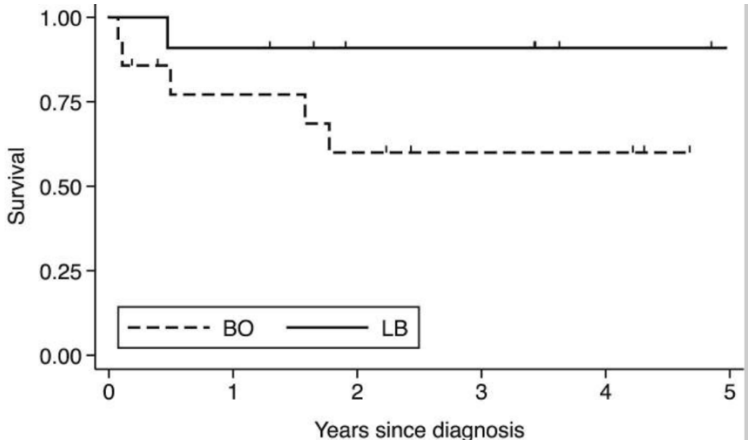
- Transition of fibroblasts into myofibroblasts with extracellular matrix overproduction (Rao 2020)
- Pro-inflammatory microbiome (Combs 2021)
- Early Th1/Th17 induced re-modelling involving neutrophils, MMP9 and IL8 (Vanaudenaerde 2007, Inamoto 2021)

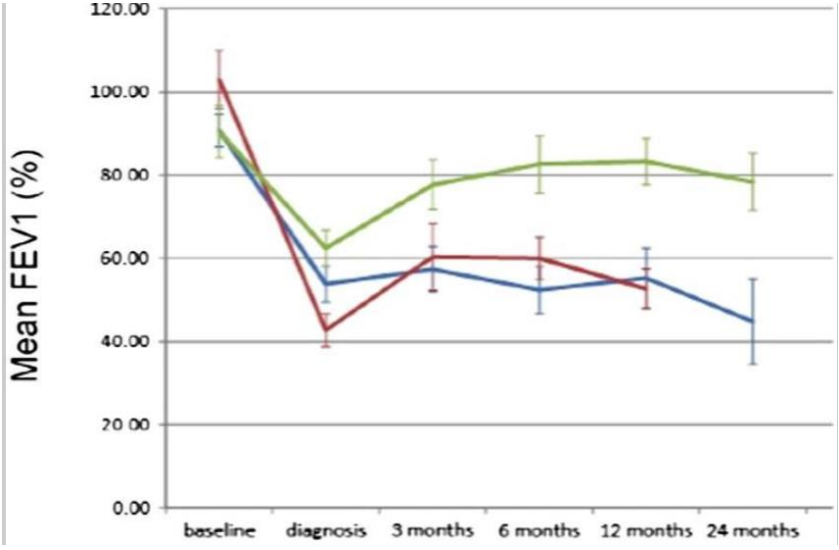
Monitoring for BOS

- PFT every 3 months through the first 2 years (day 90!)
- Afterwards every 6 months until 5 years
- Special attention should be paid in case of onset of cGVHD, progression of cGVHD at other sites or recent viral airway infection (Sheshadri 2919)
- In case of 10% decline of FEV1 start complete work up with chest CT scan (in expiration) and BAL (rule out other or concomitant causes) especially in case of early onset or rapid progression (Hildebrandt 2011)
- Treatment of BOS requires response assessment with PFT within a 3 month interval (10% decline of FEV1 indicates progressive BOS) with early BOS require shorter monitoring intervals (ERN guideline 2023)
- If classic PFT is not available consider hand held devices (Turner 2021)

Biology of BOS – possibly distinct phenotypes (Holbro B&BMT 2013)

- BOS may present with 2 subtypes – constructive bronchiolitis with primary fibrosis lacking lymphocytic infiltration and lymphocytic bronchiolitis
- Prognosis and response to steroids are significantly different
- Constrictive bronchiolitis purely responds to CNI, MMF and steroids
- Whether distinct biology or different phases of the disease explain the difference remains to be shown





Immunosuppressive treatment of BOS

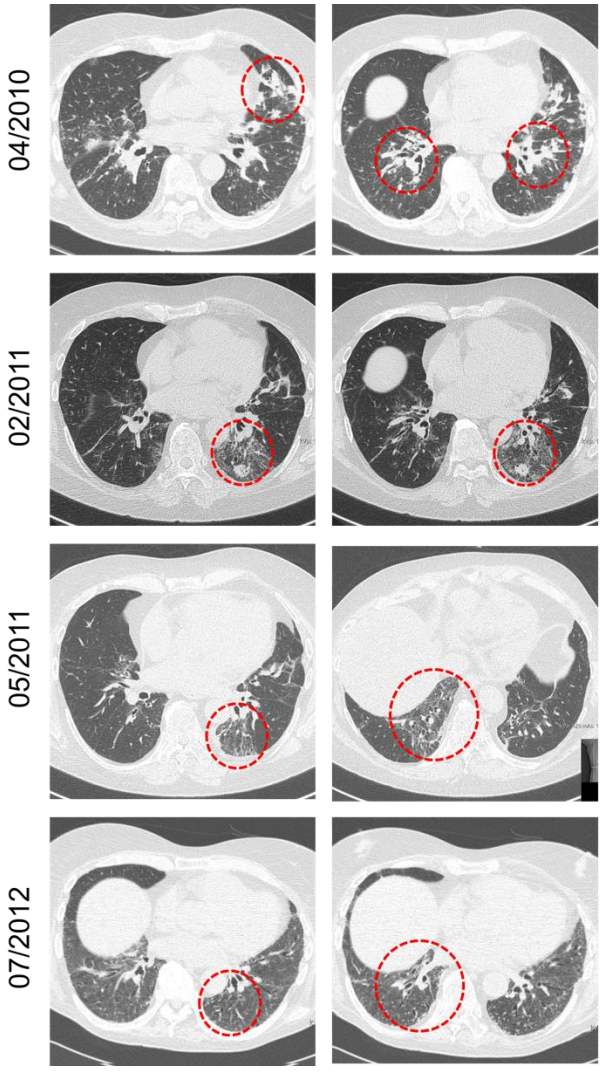
- No organ specific trials available for treatment of BOS (except FAM)
- FAM represents standard of care in pulmonary cGVHD
- Supported agents are: steroids, ECP, ruxolitinib, MMF, mTOR-inhibitors, belumosudil, abatacept, ibrutinib, CNI (Tacro > CsA), imatinib, axatilimab
- Destructing chronic infections may be treated with interferon gamma either inhaled or s.c. (Ammer 2011)
- Fibrosing components may be also treated with pirfenidon or nintedanib (Matthaiou 2022, Kouroki, M. 2021)

Restrictive pulmonary cGVHD (Cuvelier 2023)

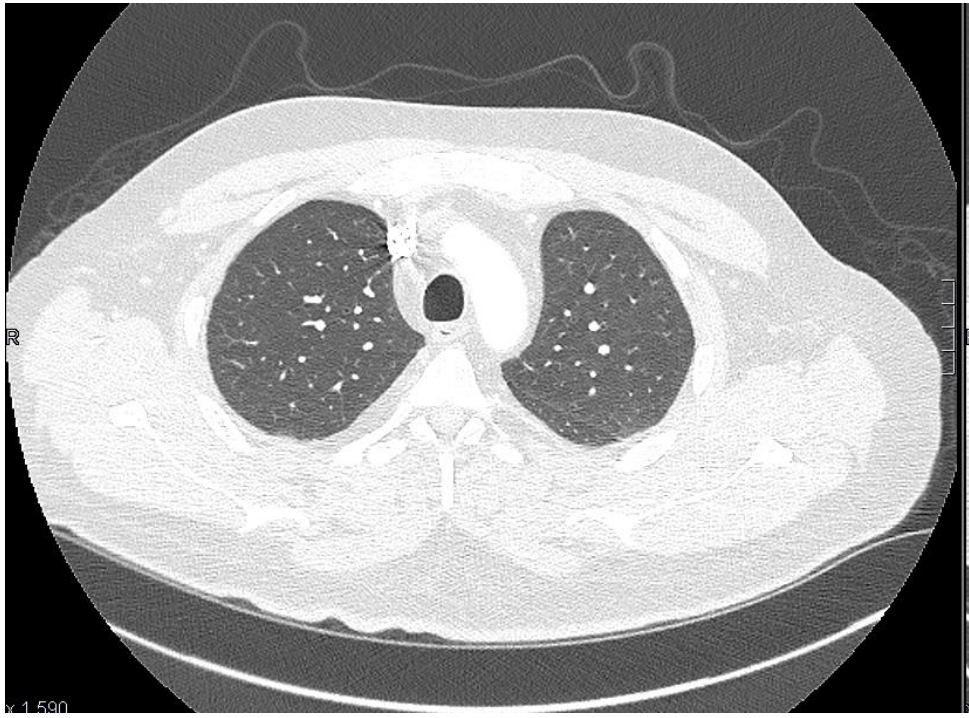
Organizing pneumonia	Restrictive impairment with reduced TLC with FEV_1/FVC > LLN with patchy and peribronchial infiltrates or consolidation, and reticular ground glass opacities, responding to corticosteroids
Non-specific interstitial pneumonia	Reduced TLC and DLCO including a decrease of FEV1 > 10% from baseline and a FEV1/FVC > 0.7 excluding extrapulmonary and infectious causes with confluent bilateral lower lobe ground glass opacities, bronchiectasis and lower lobe volumes loss
Pleuroparenchymal pulmonary fibroelastosis	Reduced TLC and DLCO, including a decrease of FEV1 > 10% from baseline and a FEV1/FVC > 0.7 excluding extrapulmonary and infectious cause, upper lobe fibrosis with subpleural and pleural thickening, loss of lung volume, and lower lobe traction bronchiectasis

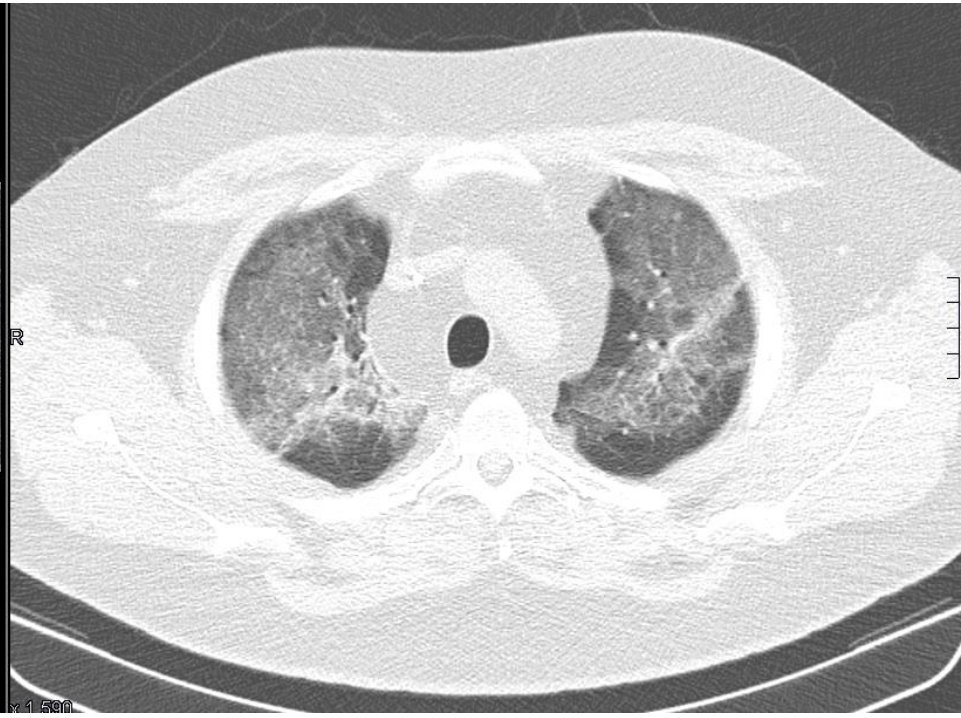
Restrictive pulmonary cGVHD (Doering & Fante 2023)

- 9 patients with restrictive pulmonary cGVHD (organizing pneumonia (OP) n=5, OP with transition into NSIP n=3, OP-like n=1)
- Risk factors: DLI, male gender, prior history of smoking
- late onset
- Mortality of NSIP was high (2 out of 3)
- Treatment required multiple lines



Lung





April 2022
after treatment
with pulsed cyclophosphamide
Followed by in vitro expanded
donor Tregs

September 2020
after failure of steroids, CNI,
Ruxolitinib, mTOR, Tocilizumab,
ECP, Interferon gamma

Conclusions

- lung manifestations is one of the leading organ manifestations associated with TRM with infections being the most frequent cause
- Early intervention appears to be associated with superior outcome but requires monitoring of asymptomatic patients
- Special attention should be paid to early BOS (decline of FEV1 at day 90)
- Restrictive pulmonary cGVHD appears less frequent compared to BOS and the sequence of inflammation followed by fibrosis appears to apply in restrictive pattern as well
- Patients with risk factors (DLI, male gender, smoking history) appears to be a cohort of risk