Fibrosing Organising Pneumonia and Pleuroparenchymal Fibroelastosis

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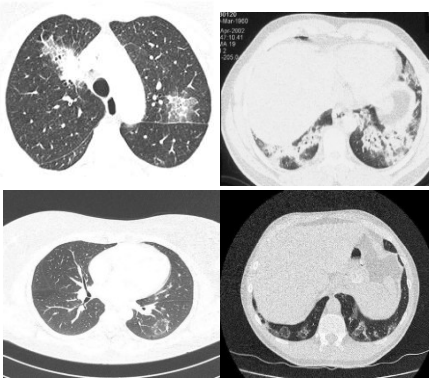
Fibrosing Organising Pneumonia and Pleuroparenchymal Fibroelastosis

- Clinical, radiological and pathological features
- Overlapping patterns
- Pathogenesis and treatment options
- Summary

Organising Pneumonia

- **Non-specific reaction pattern & inflammatory response** to acute lung injury
- **Idiopathic or secondary** (aspiration, infection, drug reaction, chemo- or radiotherapy, inhalational lung injury, CTD, hypersensitivity pneumonitis, vasculitis, NSIP, eosinophilic pneumonia,bone marrow transplantation,acute rejection of transplanted lung)
- **In at least 50% no cause is found** -> cryptogenic organising pneumonia (COP)
- **Sub-acute presentation**
- **Bi-basal crackles**
- **Lung function tests** - restrictive; may be normal or mixed obstructive and restrictive; moderately reduced transfer factor
- **Broncho-alveolar lavage** - lymphocytosis, mild increase in neutrophils and eosinophils, mast cells, macrophages; decreased CD4:CD8 ratio in some cases with an increase in cytotoxic T cells

HRCT

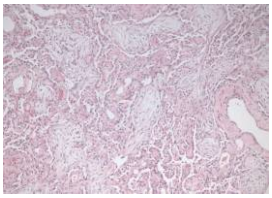


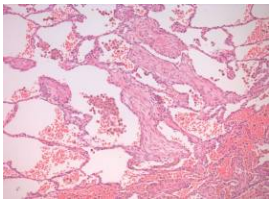
HRCT - changing multifocal peripheral consolidation, air bronchograms, ground glass opacities; predominantly sub-pleural and peri-bronchiolar; unilateral areas of consolidation, reticular changes, localised nodules

Courtesy Dr N Screaton

Pathological Features of OP

- Fibromyxoid plugs within bronchioles, alveolar ducts and surrounding alveoli; lung architecture preserved
- Fibroblasts and myofibroblasts within oedematous or myxoid, pale staining connective tissue matrix/stroma
- Mild to moderate interstitial chronic inflammation
- Re-epithelialization with epithelial cells sometimes extending over and incorporating granulation tissue plugs into interstitium
- Patchy process, temporally uniform



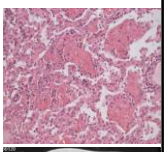


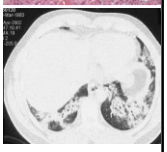
Treatment and Outcome of COP

- Good response to steroids in approximately 60-80% of patients
- Spontaneous improvement reported in some patients
- Relapse rates after treatment vary from 13-58% (Kim M, et al. 2015)
- Agents trialled in patients not responding to corticosteroids include azathioprine, cyclophosphamide, cyclosporine, mycophenolate
- Macrolides (clarithromycin, azithromycin, erythromycin) associated with response in 80% of patients (especially clarithromycin) (Radzikowska E, et al. Neuroscience and Respiration 2016)
- 10-15% experience progressive disease

Clinical-pathological Features Associated with Relapse in COP

- Multifocal fibrin deposition, indicating endothelial and epithelial damage
- Radiographic evidence of disease in all three lung zones; no relapses with solitary lung nodules
- Reduced FVC, hypoxaemia (PaO2/FiO2)
- Lack of lymphocytosis in BAL fluid
- Low serum protein and albumin levels ï underlying disease or consequence of severity of OP
- (Association with other disorders, particularly CTD)

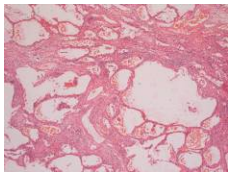


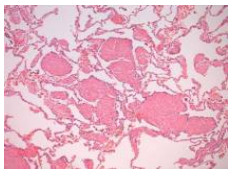


Nishimo M, et al. Human Pathology 2014
Kim M, et al. Tuberc Respir Dis 2015

Fibrosing organising pneumonia

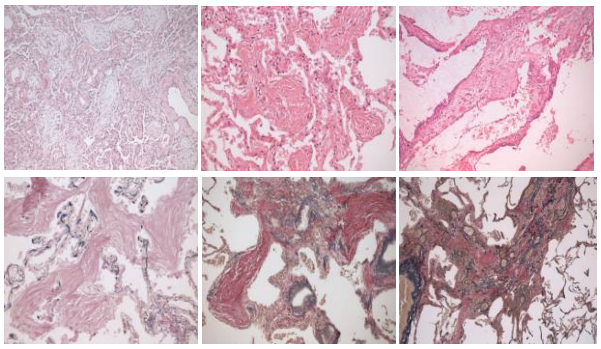
- Proportion of patients found to have some remaining disease on follow up CT scans, generally resembling a fibrotic non-specific interstitial pneumonia (NSIP) pattern
- Possible pre-existing chronic interstitial lung disease with superimposed OP reaction
- Some evidence to support progressive OP as a primary process
- Lung parenchyma remodelling with thickened, fibrotic septa
- Also an intermediate form of fibrosis with hyalinized esoinophilic plugs of connective tissue





Yousem SA, et al. Mod Pathol 1997

Fibrosing Organising Pneumonia

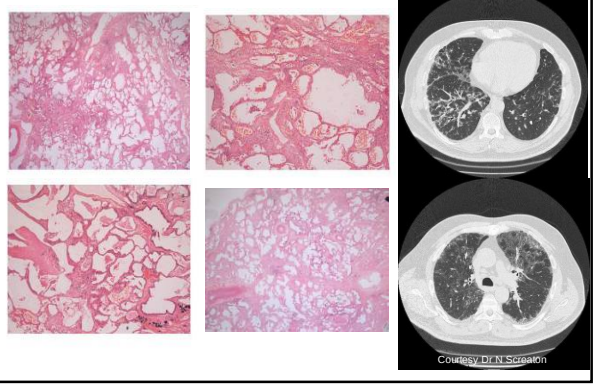


Organising pneumonia (OP)/Non-specific interstitial pneumonia (NSIP) overlap

- Histological OP ï > radiologic consolidation; focal OP; disease resolution
- Histological OP/NSIP overlap ï > GGO, reticulation, traction bronchiectasis; reactive pneumocytes; unfavourable disease progression
- Differences in the aetiology and/or degree of lung injury?
- Localized and self-limiting versus widespread and diffuse ongoing lung injury?

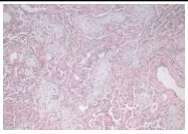
Todd NW, et al. Respiratory Medicine 2015

Organising Pneumonia / NSIP overlap?

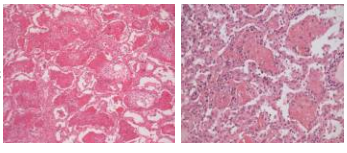


An emerging spectrum of OP?

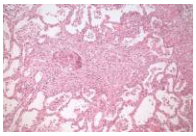
- **COP (cryptogenic organising pneumonia)**



- **AFOP (acute fibrinous and organising pneumonia))** ï intra-alveolar fibrin, reactive pneumocytes, no hyaline membranes; fulminant or subacute presentation; higher mortality; increased risk of relapse



- **GOP (granulomatous organising pneumonia)** - poorly formed granulomata associated with OP; nodules/masses radiologically; good prognosis



Patients presented similarly among all forms of OP, but AFOP patients more likely to present with fever and GOP more likely to present with lung nodules

Feinstein MB, et al. J Clin Pathol 2015
Kokosi MA, et al. Respirology 2016

Organising Pneumonia - Pathogenesis

- Circumscribed epithelial + mild endothelial injury -> death of pneumocytes and gaps in basement membrane
- Fibrinous exudate with plasma proteins and clotting factors -> activation of coagulation and fibrinolytic cascades ***(Leakage and coagulation)***
- Fibroinflammatory buds with fibroblasts which migrate through gaps in basal laminae -> formation of granulation tissue (Masson bodies) with myofibroblasts
- Re-epithelialization of basal laminae
- Mature fibrotic buds -> fewer inflammatory cells, myofibroblasts and layers of collagen (type III), fibronectin and proteoglycans ***(Organisation ---> Resorption)***

Robertson BJ, Hansell DM. Eur Radiol 2011

Fibrosing Organising Pneumonia – Disease Mechanisms

- **Inflammation**
  - **GM-CSF** on epithelial cells -> inflammatory cell recruitment
  - Inflammatory cell apoptosis and macrophage phagocytosis ï requires **CD44** expression on macrophage surface
  - Macrophages produce pro-inflammatory cytokines and pro-fibrotic factors
  - In patients with progressive fibrosis -> **TGF-β1 associated expression of protein tyrosine kinase 2 (PTK2)** by inflammatory cells (-> cell migration & adhesion between epithelial cells and ECM; fibroblast proliferation, activation and collagen production)

Schlesinger C, Koss MN. Curr Op Pulmon Med 2005
El-Zammar O, et al. Human Pathol 2009
Izykowski N, et al. J Transl Med 2016

Fibrosing Organising Pneumonia - Pathogenesis

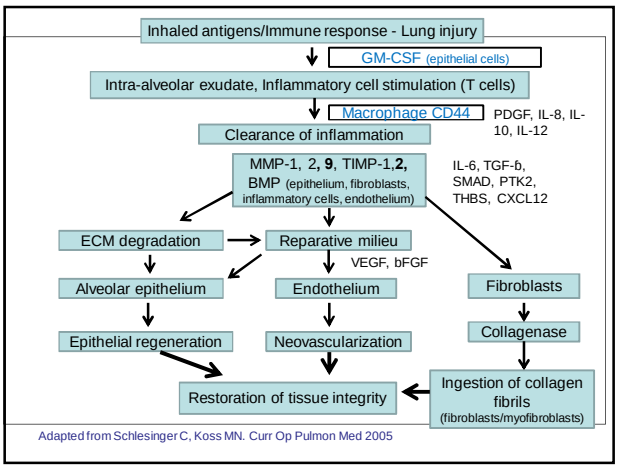
- Leukocytes and stromal cells express **IL-6** (proinflammatory), **TGF-β, downstream SMADs**, and **thrombospondin 1 (THBS1)** -> associated with collagen production, overactivation, migration and proliferation of (myo)fibroblasts
- **Profibrotic thrombospondin 1 (THBS1), SMADs and PTK2** - overexpressed in OP lesions
- **TGF-β** (Smad3 signalling) induces **epithelial-mesenchymal transition (EMT)** in alveolar epithelial cells (reversed by BMP7)
- Fibroblasts secrete **Cxcl12** (chemoattractant for T cells and monocytes) and receptor Cxcr4 is expressed by leukocytes
- **Cxcl12/Cxcl4 axis** important for generating profibrotic microenvironment

Izykowski N, et al. J Transl Med 2016
Brigham CW, Borok Z. Am J Physiol Lung Cell Mol Pysiol 2007

Fibrosing Organising Pneumonia – Disease Mechanisms

- **Matrix metalloproteinases (MMPs)**
  - Mediate ECM remodelling through degradation and re-synthesis
  - MMP/TIMP (tissue inhibitors of metalloproteinases) balance and homeostasis is crucial for normal repair and remodelling
  - Macrophages, eosinophils & neutrophils are major sources of MMP-9
  - Accumulation and persistence of collagen is dependent on **bone morphogeneic proteins (BMPs), matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs)**
  - Higher concentrations of MMP-9 and TIMP-1 in BAL of COP patients than in UIP
  - Low MMP-9:TIMP-1 ratio in UIP
  - Imbalance within at least one MMP/TIMP pair is noted in a fibrotic as compared to a reparative response

Schlesinger C, Koss MN. Curr Op Pulmon Med 2005
El-Zammar O, et al. Human Pathol 2009
Izykowski N, et al. J Transl Med 2016



Adapted from Schlesinger C, Koss MN. Curr Op Pulmon Med 2005

Organising Pneumonia – Disease Mechanisms

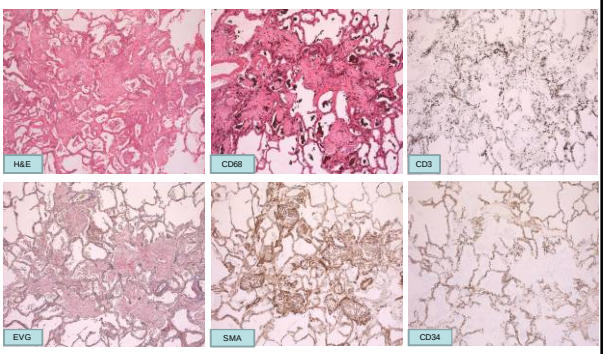
- **Granulation tissue formation & fibroblast repair**
  - Intra-alveolar fibroblastic buds -> type III collagen, no elastic fibres; surface lined by alveolar epithelial cells with discontinuous basement membranes
  - UIP matrix contains type I collagen and elastic fibres
  - Myofibroblasts within fibroblastic buds express matrix metalloproteinase (MMP)
  - Myofibroblasts in UIP have high levels of TIMP-2
  - Neovascularization stimulated by VEGF occurs within connective tissue of OP and regenerating endothelial cells are positive for MMP-2
  - No neovascularization in UIP
  - Apoptotic activity in fibromyxoid lesions
  - Apoptotic activity is lower in UIP than in COP

Schlesinger C, Koss MN. Curr Op Pulmon Med 2005
Lappi-Blanco E, et al. Lung 1999

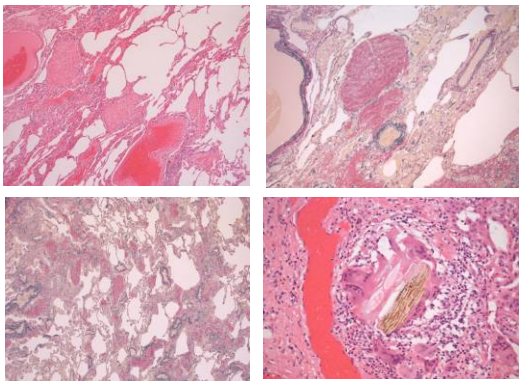
Reversible Organising Pneumonia

- **Prominent neovascularizationof intra-alveolar buds** (VEGF and bFGF and receptors for VEGF expressed in granulation tissue in OP) (Popper HH. Verh Dtsch Ges Path 2002; Lappi-Blanco E, et al. J Pathol 2002)
- **Predominance of type III collagen – loose matrix susceptible to degradation** (type I collagen encountered in fibrotic lung disease, eg UIP) (Robertson JB, Hansell DM. Eur Radiol 2011)
- **Fibrin negative, SMA negative Masson bodies had complete resolution** (Yoshinouchi et al. Resp Med 1995)
- **Increased apoptotic activity within fibromyxoid buds in OP** (Lappi-Blanco E, et al. Lung 1999)
- **Alveolar re-epithelialization** (Cordier J-F. Eur Respir J 2006)

Fibrosing Organising Pneumonia



Fibrosing Organising Pneumonia



Recurrent/Refractory COP – Treatment Options

- **Macrolides (clarithromycin, azithromycin)**
  - **non-specific anti-inflammatory, rather than antibiotic, activity in COP**
  - **↓ serum concentration of IL-6, IL-8 (neutrophil chemoattractant) and TGF-β in patients who responded to treatment**
  - **Dose dependent suppression of BAL levels of TNF-α, sTNFR2, IL-6, IL-8 and CCL18 (T cell chemoattractant) produced by alveolar macrophages**
  - **Macrolides in combination with steroids may be used in cases of refractory or recurrent COP**
- **Mycophenolic acid treatment**
- **Cyclosporine and cyclosporine A**

Cai M, et al. Immunobiology 2013
Ding QL, et al. Experimental and Therapeutic Medicine 2015
Paul C, et al. Respiration 2016
Kobayashi T, et al. Intern Med 2017

Organising Pneumonia - Summary

- Non-specific response to acute lung injury – cryptogenic or secondary
- ***Pathogenesis*:** multifactorial, involving altered immunity, inflammation, infection, drugs
- ***Imaging*:** changing multifocal consolidation with or without reticular changes
- ***Histology*:** fibroinflammatory exudates -> plugs of granulation tissue -> resorption and restoration of lung architecture

Fibrosing Organising Pneumonia - Summary

- Abnormal healing with
  - imbalance of coagulation and fibrinolytic cascades
  - increased proinflammatory and profibrotic cytokines
  - imbalance of MMPs and TIMPs
  - increase in myofibroblasts (via TGF-b)
  - reduced angiogenic growth factors (VEGF, bFGF)

  -> cross-talk between numerous pathways
  -> bidirectional signalling between alveolar epithelial cells, fibroblasts, endothelial cells
  -> genetic host factors
- Macrolide therapy – anti-inflammatory and possible anti-fibrotic effects

Pleuroparenchymal Fibroelastosis (PPFE)

- 1992 Amitani et al. – "*upper lobe pulmonary fibrosis/Amitani's disease*"
- 2004 Frankel et al. – "*pleuroparenchymal fibroelastosis*"

- Included in 2013 update of IIP classification as a rare idiopathic interstitial pneumonia (?form of chronic lung injury seen in association with a variety of clinical-pathological conditions)
- Distinctive array of clinical, imaging and pathological abnormalities

- Predominantly upper lobe visceral pleural fibrosis, subpleural intra-alveolar fibrosis and alveolar wall elastosis

Pleuroparenchymal Fibroelastosis (PPFE)

- Adults; median age 57 years; no gender predilection
- Bimodal distribution of presentation (3rd and 6th decades)
- No association with smoking (85% never smokers)
- More frequently described by Japanese groups (5.9% of interstitial pneumonia (Nakatani T et al. Eur Respir J 2015); more elderly male patients)

- SOB, dry cough, weight loss, platythorax, pneumomediastinum, spontaneous unilateral or bilateral pneumothoraces (30%), which may complicate biopsy procedures
- Restrictive pulmonary physiology

- Variable disease course – progressive in many cases
- PPFE in association with transplantation seems to have a worse prognosis
- Serum biomarkers – elevated SP-D, KL-6 increases only as disease progresses, serum autoantibodies (ANA, RhF)

Reddy TL, et al. Eur Respir J 2012
Kokosi MA, et al. Respirology 2016
von der Thusen JH. Curr Resp Med Rev 2013
Bonifazi M, et al. Curr Pulm Rep 2017
Watanabe K. Curr Resp Med Rev 2013

Entities Associated with PPFE

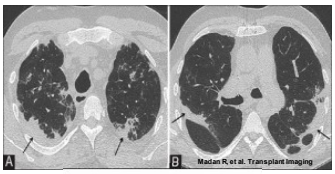
- **Bone marrow transplantation** *(~6%)*
- **Lung transplantation** *(50%) - possible pathological phenotype of restrictive allograft syndrome (RAS) – late complication in 7.5% of lung transplants*
- **Chemotherapy** *(10%) (time between end of CTx and clinical symptoms 1-16 years)*
- **Radiotherapy**
- **Respiratory infections** ***(recurrent infections in 50%)*** – *recurrent bronchitis, Aspergillus, MAI*
- **Autoimmune diseases** – *RA, ankylosing spondylitis, ulcerative colitis, psoriasis,*
- **Exposures** – *asbestos, aluminium*
- **Hypersensitivity pneumonitis**
- **Familial PPFE** *(family history of pulmonary fibrosis 9%)*

- **10-30% of cases are idiopathic**

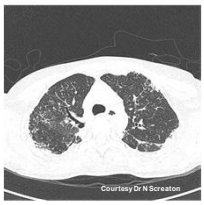
Portillo K, et al. Arch Bronconeumol 2015
Reddy TL, et al. Eur Respir J 2012
Kokosi MA, et al. Respirology 2016
Bonifazi M, et al. Curr Pulmon Rep 2017
Hurtado EJS, et al. Chronic Resp Disease 2016
Beynat-Mauterde C, et al. Eur Respir J 2014
Camus P, et al. Interstitial and Orphan Lung Disease 2014

PPFE – Imaging and Pathology Findings

- **Imaging**
  - **Pleural thickening** in upper zones
  - **Subadjacent parenchymal fibrosis** (reticular & nodular opacities), extension along septa
  - In advanced stages - **traction bronchiectasis, bullae & cysts**
  - Clear demarcation between abnormal and normal lung
  - Hila retracted upwards



  - ILD pattern in other zones
    - More diffuse PPFE, NSIP, UIP, unclassifiable IP
  - Other features
    - Bronchiectasis, consolidation



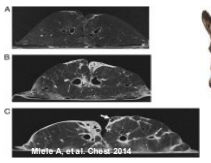
Reddy TL, et al. Eur Respir J 2012
Cheng SKH & Chuah KL. Arch Pathol Lab Med 2016
Bonifazi M, et al. Curr Pulmon Rep 2017

Pleuroparenchymal Fibroelastosis (PPFE)

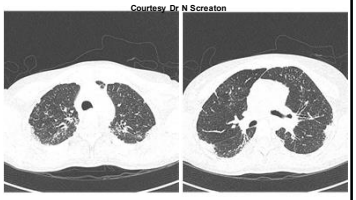
HRCT Imaging Criteria

- **'Definite'**
  - **Upper lobe pleural thickening and subpleural fibrosis**
  - Lower lobe involvement less marked or absent

- **'Consistent with'**
  - **Upper lobe pleural thickening and subpleural fibrosis, but distribution of changes not concentrated in upper lobes** (equal involvement of upper & lower lobes in 1/3 of cases), or
  - presence of **features of coexistent disease elsewhere**



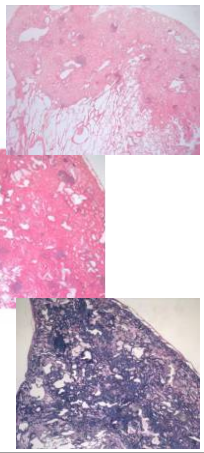
Courtesy Dr N Screaton



von der Thusen JH. Curr Resp Med Rev 2013
*Miele A, et al. Chest 2014

Histological Criteria

- **'Definite'**
- **Upper zone fibrosis of the visceral pleura**, and
- **Subpleural intra-alveolar fibrosis** with **interstitial elastosis**
- Sparing of the parenchyma distant from the pleura (sharp transition to unaffected lung)
- Mild, patchy lymphoplasmacytic infiltrates,
- Small numbers of fibroblastic foci

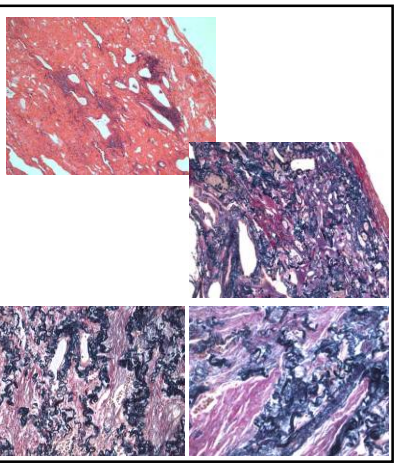


- **'Consistent with'**
- Intra-alveolar fibrosis as above, but
  - Not associated with significant pleural fibrosis, or
  - Not predominantly beneath the pleura, or
  - Not in a upper lobe biopsy

von der Thusen JH. Curr Resp Med Rev 2013

Â Proposed criteria ï
ïmultilobar or subpleural and/or centrilobular fibrosing IP characterized by extensive (>80%) proliferation of elastic fibres in non-atelectatic lung with absent or scant chronic inflammation and no or rare granulomasò

Hirota et al. Eur Resp J 2013;
Rosenbaum JN, et al. Human Pathol 2015



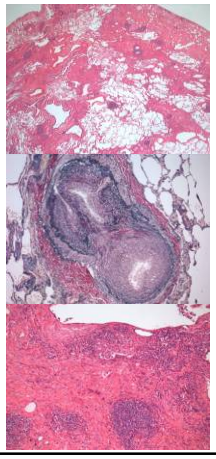
Histology

ÂOther changes
- ï Bronchocentric intra-alveolar fibrosis and elastosis (IAFE), perilobular IAFE

ÂCo-existent ILD in lower lobes
- ï IAFE, IAFE and HP, UIP** (25% - up to 75% in some series)

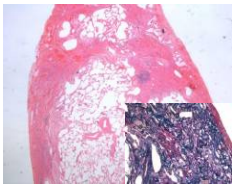
ÂOther features
- ï Venous and arterial intimal fibrosis
- ï Granulomas; non-specific infammation, focally with lymphoid follicle formation
- ï (Telangiectatic erythematous cutaneous eruption ï perivascular infiltrate & increase in elastic fibres*)

Reddy TL, atypical et al. Eur Respir J 2012
Nakatani et al. Eur Respir J 2015
*Lowther CM, et al. Am J Dermatopathol 2016
**Oda T, et al. Chest 2014



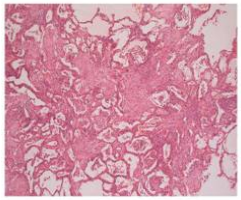
Differential Diagnoses of PPFE

- Usual interstitial pneumonia (UIP) ï idiopathic (IPF) or secondary to known causes
- Combined UIP and PPFE* (poorer outcome than PPFE or UIP alone**)
- Non-specific interstitial pneumonia
- Asbestosis
- Advanced fibrosing sarcoidosis
- Radiation-induced lung disease
- Apical caps
- Fibrosing organising pneumonia

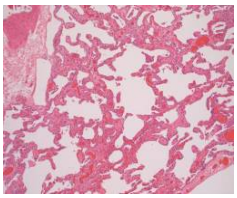


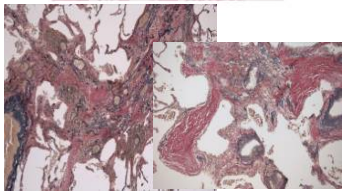
Cheng SKH, Chuah KL. Arch Pathol Lab Med 2016
**Oda T, et al. Chest 2014
*Enomoto N, et al. BMC Pulmonary Medicine 2014

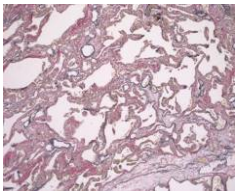
Fibrosing organising pneumonia



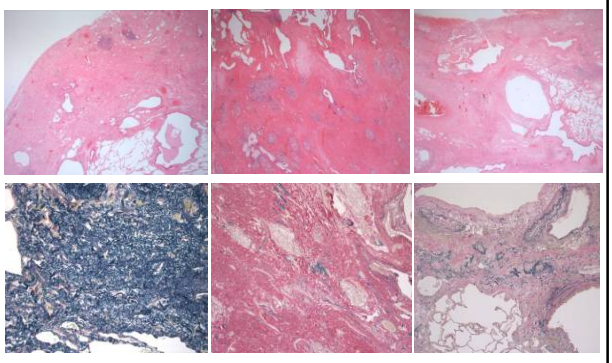
NSIP







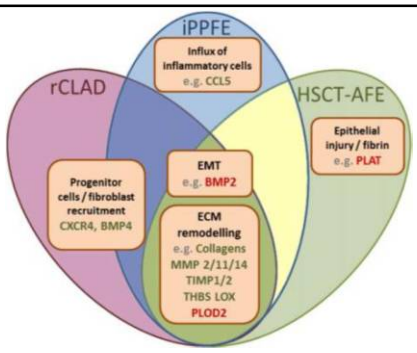
Apical cap | Sarcoidosis with fibrosis | UIP



Aetiology and Pathogenesis

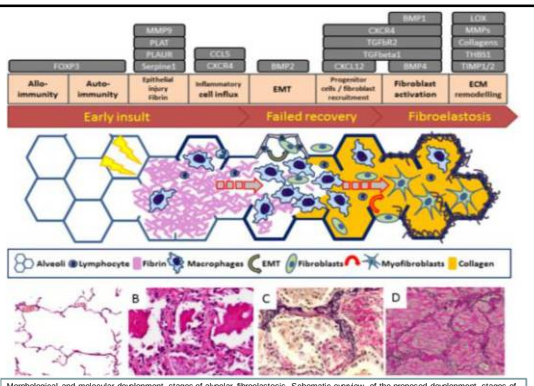
- Alveolar fibroelastosis (AFE) ï a reaction to injury pattern
- Elastin destruction (eg. release of elastolytic proteases by inflammatory cells) -> reactivation/upregulation of elastin synthesis but in a disordered manner
- Elastosis is transcriptionally regulated
  - ï Elastin gene expression increase following lung injury in certain animal models
  - ï TGF-Ü upregulation caused pleural and parenchymal fibrosis and elastosis in murine model
  - ï Elastin mRNA within cells of muscularis of conducting airways and scattered interstitial cells

Rozin GF, et al. Histopathology 2005
Negri EM, et al. Histopathology 2000
Huang Z, et al. Int J Clin Exp Pathol 2015
Becker CD, et al. Mod Pathol 2008



Comparative analysis of expression profiles of AFE pattern in rCLAD, HSCT (haemopoeitic stem cell transplantation) and iPPFE. Upregulated genes are shown in green and downregulated genes in red. The majority of genes are expressed equally in AFE independent of clinical background. These genes regulate ECM remodeling and EMT. Individual differences in gene expression were found on the level of fibroblast/progenitor cell recruitment, influx of inflammatory cells and response to fibrin.

From Jonigk D, et al. The Journal of Pathology, January 2017



Morphological and molecular development stages of alveolar fibroelastosis. Schematic overview of the proposed development stages of alveolar fibroelastotic remodelling from early to late events and corresponding histopathological images. The grey boxes indicate the analysed genes in conjunction with their respective functions in the context of alveolar fibroelastosis; an early insult with or without participation of allo and/or autoimmunity, followed by fibrin rich exudates in the alveolar lumen (fibrin stage), leads to a futile resolution by macrophages (histiocytic stage) and results in fully remodelled alveolar fibroelastosis.

From Jonigk D, et al. The Journal of Pathology, January 2017

Telomere-related Gene Mutations

- **Mutations in telomere machinery maintenance genes** (telomerase reverse transcriptase (TERT), telomerase RNA component (TERC), regulator of telomere elongation helicase 1 and poly(A)-specific ribonuclease) **lead to variable interstitial lung disease**
- TERT & TERC mutations -> pulmonary fibrosis through low telomerase activity, accelerated telomere shortening, exhaustion of lung stem cells
- **~10% of PPFE cases** found to have genetic aberrations
- TERT mutations identified in 50%; female predominance
- **Importance of searching for telomere-related gene mutations and short telomere syndrome** in patients with PPFE, even without a family history
- Telomerase activity and length are modified in various systemic immune-mediated diseases

Nunes H, et al. Eur Respir J 2017
Traila D, et al. Pneumologia 2015

Telomere-related Gene Mutations

- Patients with telomere-related gene mutation ï > predisposition to tractional injury in peripheral lung
- Mutations of TERT & TERC in 19% of pulmonary fibrosis cases; additional environmental, genetic, epigenetic factors contribute to telomere erosion and disease phenotype
- Lung injury -> extracellular matrix responds with remodelling of all of its components
- Differential degree of elastosis and collagen fibroproliferation between upper and lower lobes may be due to different lung zones subjected to different mechanical strains

Nunes H, et al. Eur Respir J 2017
Traila D, et al. Pneumologia 2015

Restrictive Allograft Syndrome (RAS) and PPFE

- **Concomitant OB in RAS cases**
  (BO, pneumothorax and PPFE suggested to be airway related diseases in BMT patients with GVHD (Fujikura Y, et al. Int Med 2014
  PPFE may also represent persistence of intra-alveolar organisation (von der Thusen JH, et al. Mod Pathol 2011))
- **Vascular fibrointimal thickening with lymphoplasmacytic infiltration** in RAS cases (Montero MA, et al. Histopathology 2017)
- Slight reduction of capillary network in RAS cases (?due to capillary vascular injury)
- **Diffuse alveolar damage (with thromboemboli) may precede RAS** (Sato M, et al. JHLT 2012; Ofek E, et al. Mod Pathol 2012)
- (Thromboembolic arteriopathy found in PM case of PPFE (van der Oord K, et al. Pathol Int 2017))
- **Immunological mechanisms (eg. AMR)**
- **Vascular changes in PPFE**
- **Recurrent infection/CMV** ï risk factor for CLAD (Mariani F, et al. Diagn Interv Radiol 2016)
- **RAS and PPFE histopathology shows IAFE and fibro-inflammatory vascular changes, which may be important in the pathogenesis of IAFE** (Montero MA, et al. Histopathology 2017)

PPFE - Treatment Options

- Low or high dose corticosteroids
- Cyclophosphamide, azathioprine
- N-acetylcysteine
- Antibiotics (azithromycin) ï for recurrent infections
- Pirfenidone
- Lung transplantation

Sato S, et al. Intern Med 2016
Reddy TL, et al. Eur Respir J 2012
Kokosi MA, et al. Respirology 2016
Bonifazi M, et al. Curr Pulmon Rep 2017

Pleuroparenchymal Fibroelastosis - Summary

- Distinct pattern of chronic lung injury, influenced by genetic factors – starting point may involve acute lung injury or interstitial inflammation
- IAFE is not specific to PPFE (can be seen following radiotherapy, chemotherapy, inhalational injury)
- Clinical data suggest link to recurrent infection
- Genetic and autoimmune mechanisms may contribute - repeated inflammatory injury due to immune dysregulation
- PPFE may also present with more diffuse involvement and co-exist with different patterns of ILD (UIP, NSIP, HP)
- Patients may have a genetic predisposition to lung fibrosis (eg. telomere-related gene mutations), which may manifest as different histopathological patterns of fibrosing lung disease