Banner University Medicine

Intro to ILD
IM Residency Lecture

Stephanie Iusim MD, MPH

Assistant Professor of Pulmonary

3.15.22

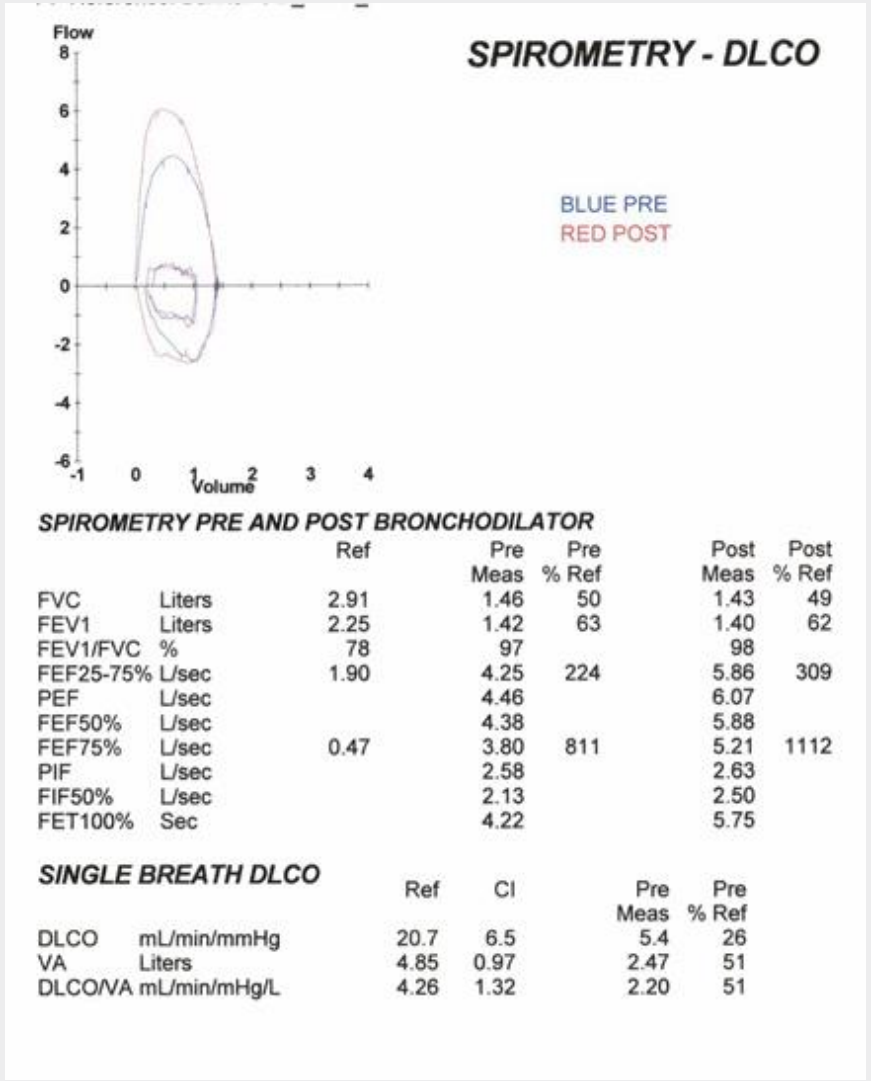
Goals of this lecture

1. Be able to define ILD
2. Understand the basic types of ILD
3. Understand the evaluation and management

Case 1 Part A

75 year old male presents with exertional dyspnea x 1 year. He reports an associated dry cough that has increased in intensity over the past few months. He has some trouble walking on inclines or up flights of stairs. His vitals T 37 HR 95 BP 130/80 Sp02 93% on RA RR 20. Physical examination is notable for bibasilar crackles. Spirometry is shown on the next slide. 6 minute walk test saturation nadir 88%, walked 400 meters (normal >576 meters) . He denies occupational/environmental exposures or hx of autoimmune disease. Medications include: lisinopril, atorvastatin and baby aspirin. CXR shows bibasilar interstitial lung markings concerning for interstitial lung disease. You are concerned about ILD. What is the best next step?

Case 1 Part A



SPIROMETRY - DLCO

BLUE PRE
RED POST

SPIROMETRY PRE AND POST BRONCHODILATOR

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref
FVC	Liters	2.91	1.46	50	1.43	49
FEV1	Liters	2.25	1.42	63	1.40	62
FEV1/FVC	%	78	97		98	
FEF25-75%	L/sec	1.90	4.25	224	5.86	309
PEF	L/sec		4.46		6.07	
FEF50%	L/sec		4.38		5.88	
FEF75%	L/sec	0.47	3.80	811	5.21	1112
PIF	L/sec		2.58		2.63	
FIF50%	L/sec		2.13		2.50	
FET100%	Sec		4.22		5.75	

SINGLE BREATH DLCO

		Ref	CI	Pre Meas	Pre % Ref
DLCO	mL/min/mmHg	20.7	6.5	5.4	26
VA	Liters	4.85	0.97	2.47	51
DLCO/VA	mL/min/mHg/L	4.26	1.32	2.20	51

Case 1

What is the best next step?

1. Repeat CXR in 1 month to see if these findings are persistent and then consider a ct scan of the chest
2. Obtain a High resolution CT scan of the chest
3. Refer to Pulmonary for evaluation
4. Refer for surgical lung biopsy

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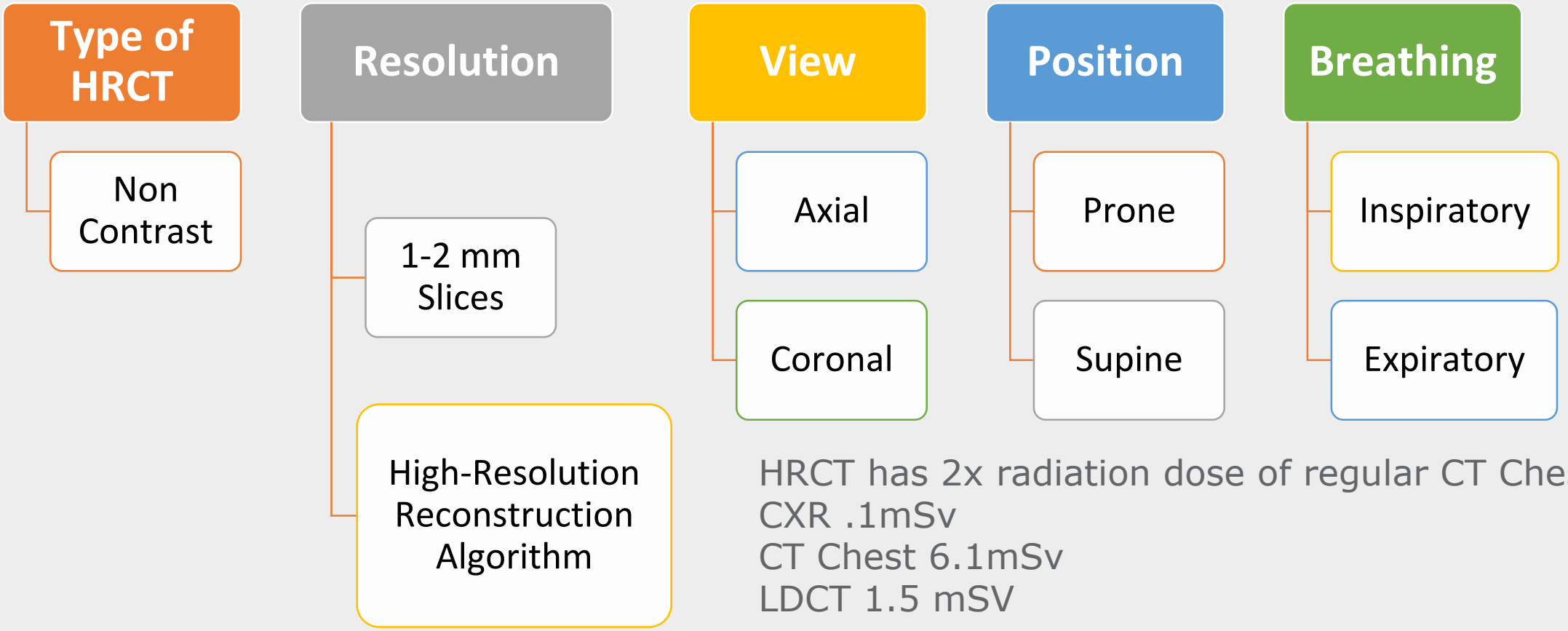
Features of HRCT



HRCT has 2x radiation dose of regular CT Chest
CXR .1mSv
CT Chest 6.1mSv
LDCT 1.5 mSV

Courtesy of Dr Padilla

ILD/Diffuse Parenchymal Lung Disease

What is ILD?

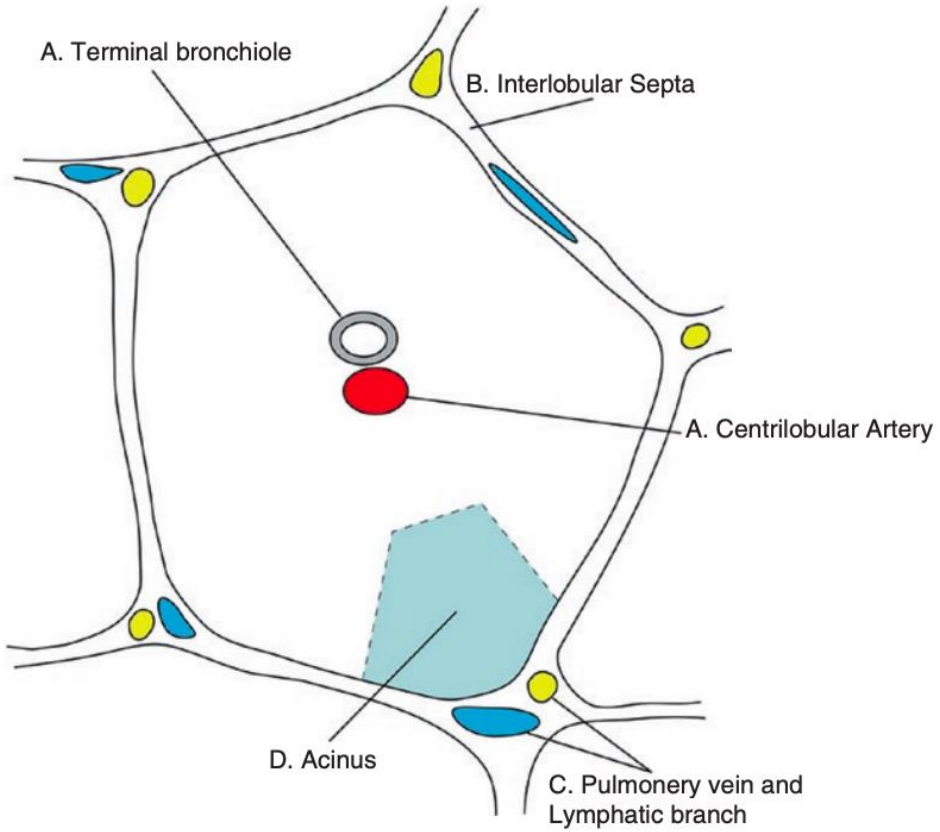


Fig. 1 Secondary pulmonary lobule (*A*: Centrilobular arteries and bronchioles with a diameter of approximately 1 mm; *B*: Interlobular septa with a thickness of approximately 0.1 mm; *C*: Pulmonary vein and lymphatic branch with diameters of 0.5 mm each; *D*: Acinus—never visible on CT scans)

ILD can impact:

Peribronchovascular Interstitium

Intralobular/interlobular interstitium

65% of ILD is Idiopathic

Mueller-Mang et al. Interstitial Lung Diseases. Med Radiol Diagn Imaging 2017

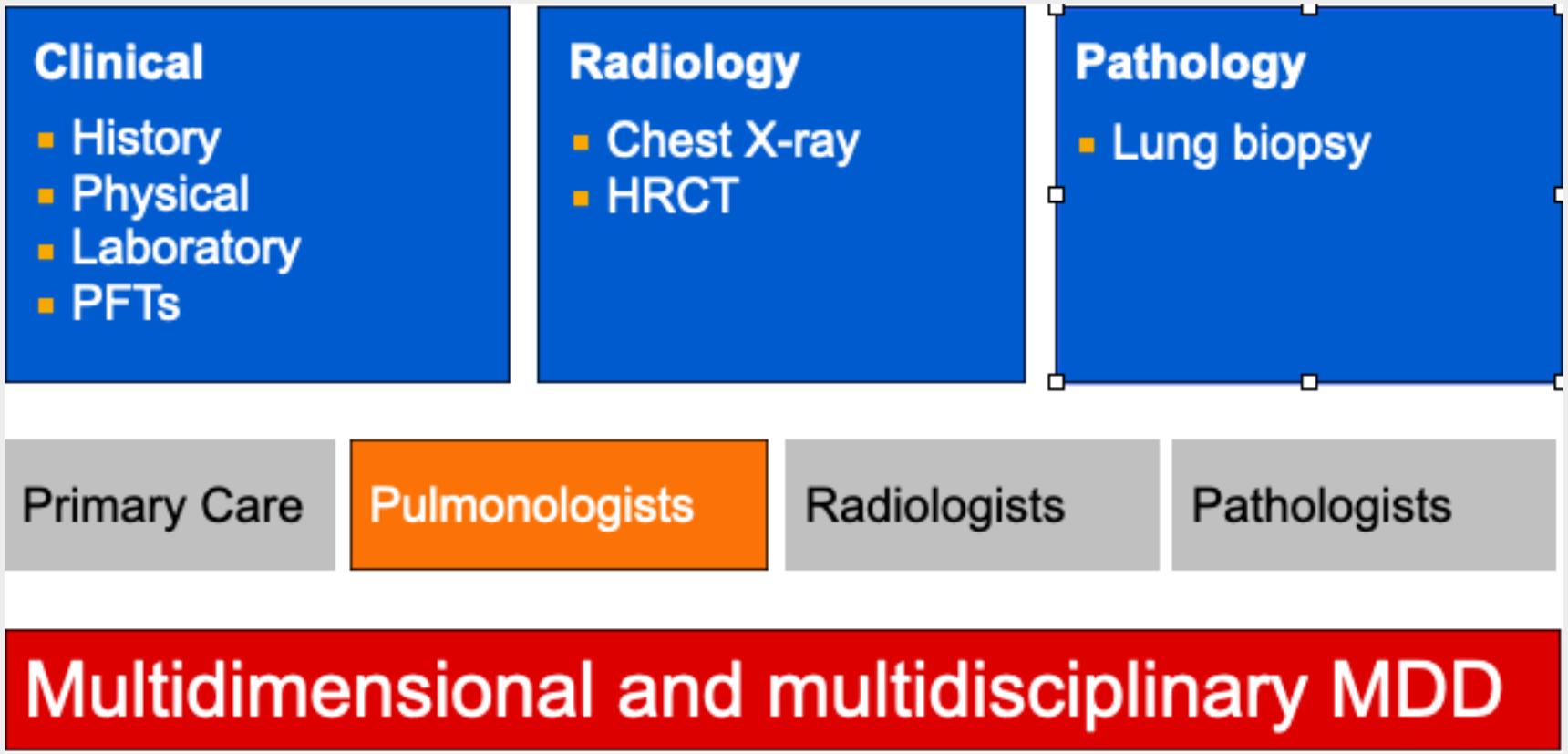
Diagnosis

Connective Tissue Disease	Drug	Environmental	Sarcoidosis	Idiopathic
Rheumatoid Arthitis Scleroderma SLE Sjogren's MCTD PM/DM	Amiodarone Nitrofurantoin Chemotherapy Radiation "pneumotox.com"	Molds Birds Asbestos Silica Coal dust Farm (cotton picking)		IPF iNSIP RB-ILD DIP COP AIP

HRCT Patterns and Pathology

Connective Tissue Disease	Drugs	Environmental	Idiopathic
Nonspecific interstitial pneumonia = NSIP		Chronic Hypersensitivity Pneumonitis Pneumoconioses	IPF-Usual interstitial pneumonia (UIP) iNSIP= NSIP RB-ILD DIP COP = organizing pneumonia AIP = DAD

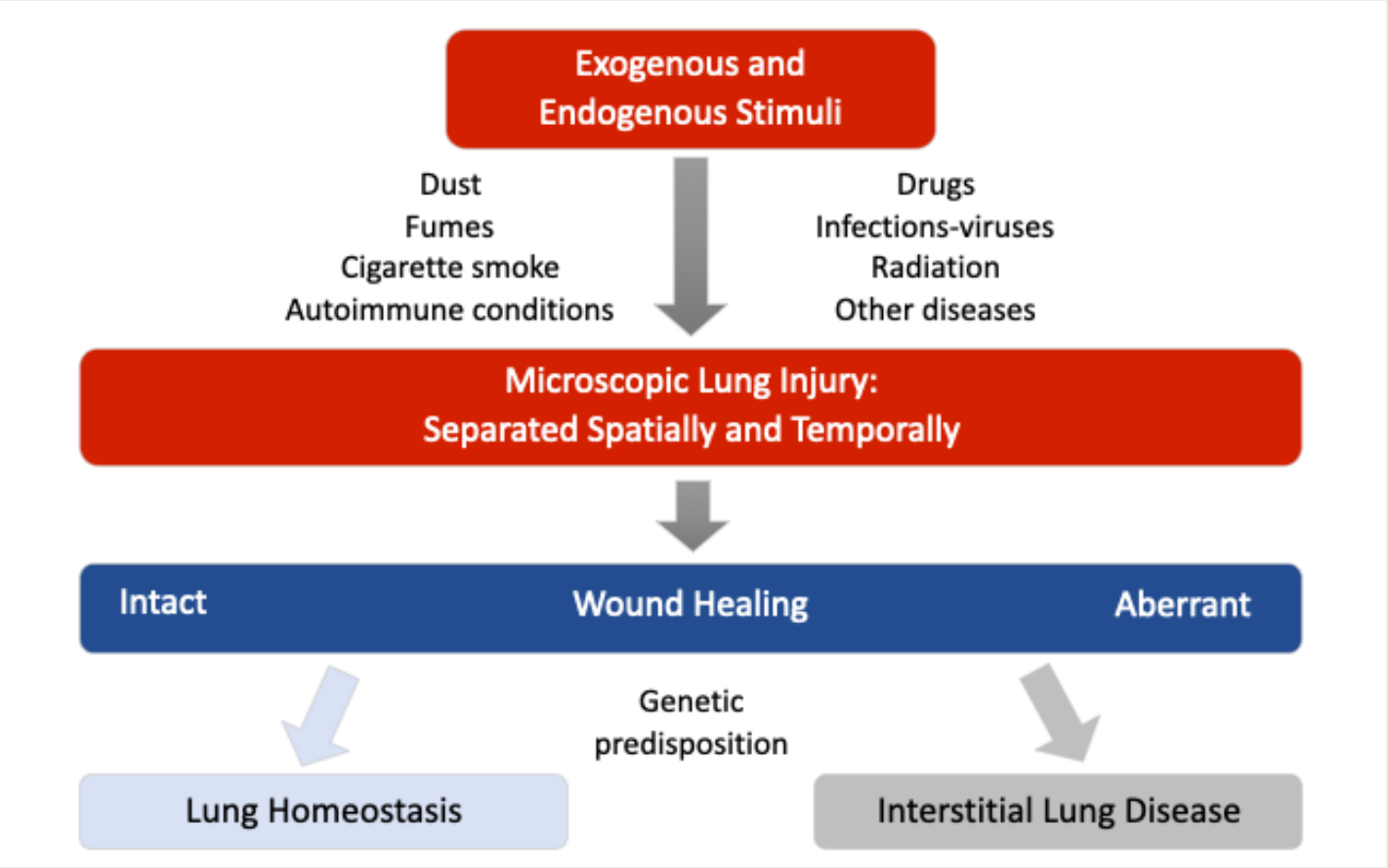
Approach to the Diagnosis of ILD



Modified from American Thoracic Society. *Am J Respir Crit Care Med.* 2002;165:277-304.

Courtesy of Dr Padilla

Pathophysiology of ILD

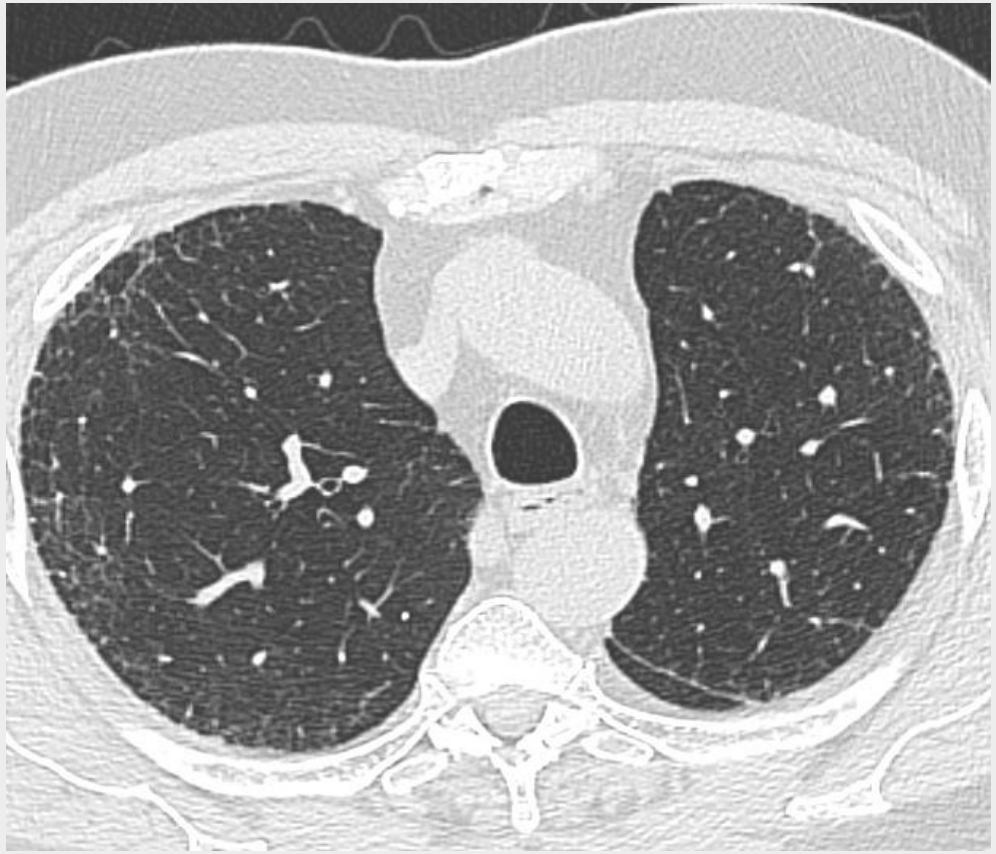


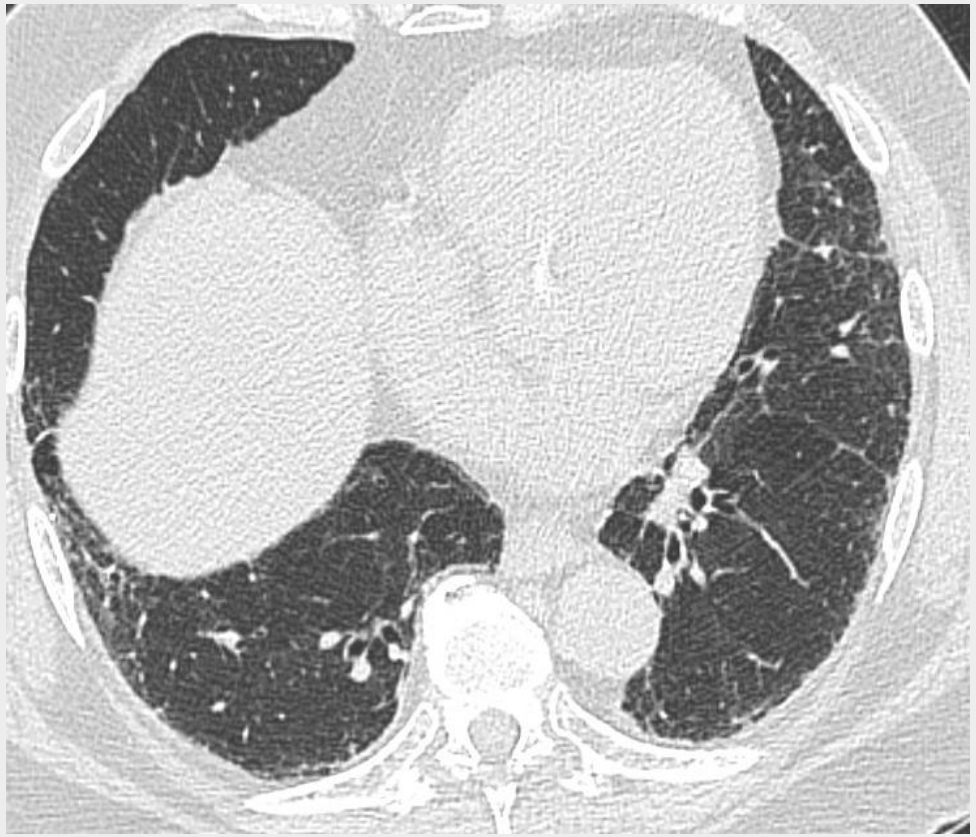
Steele MP, Schwartz DA. *Annu Rev Med.* 2013;64:265-276.

Courtesy of Dr Padilla

Case 1 Part B

You obtain a High resolution CT scan of his chest.





Case 1 Part B

What is the most likely diagnosis?

1. idiopathic NSIP
2. Idiopathic Pulmonary Fibrosis
3. Chronic Hypersensitivity Pneumonitis
4. Organizing Pneumonia

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What is the most likely diagnosis?

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IPF

Definition (ATS/ERS 2018):

- "Chronic, progressive, fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults and limited to the lungs"

- Most common IIP and ILD
- Prevalence 50 per 100,000
- Median survival is 3 years
- Histopathologic/Radiologic pattern:
  - Usual interstitial pneumonia (UIP)
- Genetics: TERT/TERC mutations and MUC5B
- Demographics:
  - M>F
  - Age 50s-60s
  - Hx of smoking

IPF

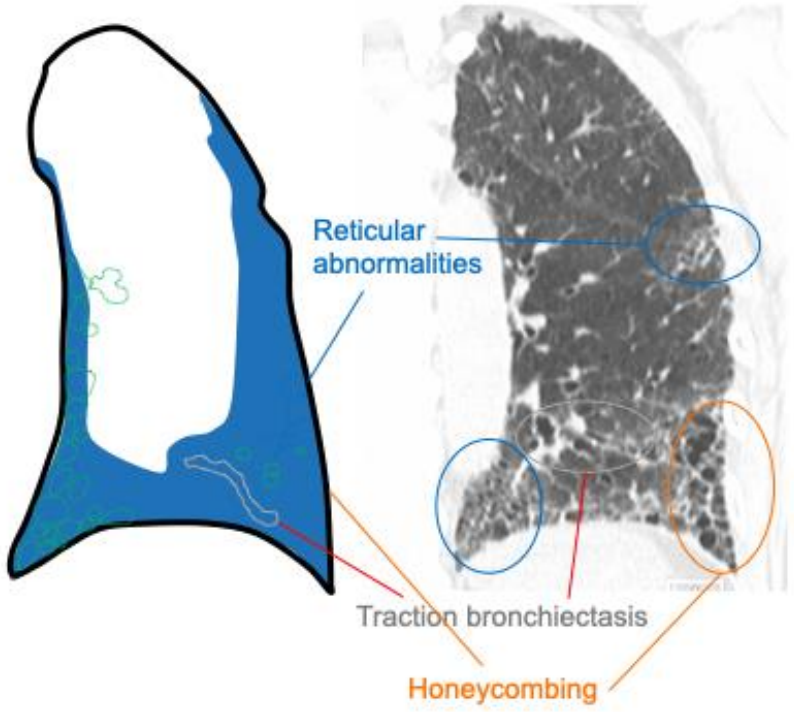
Summary: ATS Diagnostic Criterion

Using HRCT to Detect the Pattern of Usual Interstitial Pneumonia[1]

Definitive UIP Pattern[1]

- Subpleural, basal predominance
- Reticular abnormality
- Honeycombing with or without traction bronchiectasis
- Absence of features listed as inconsistent with UIP pattern

UIP Distribution and Pattern in a Patient's Lung[2,a]

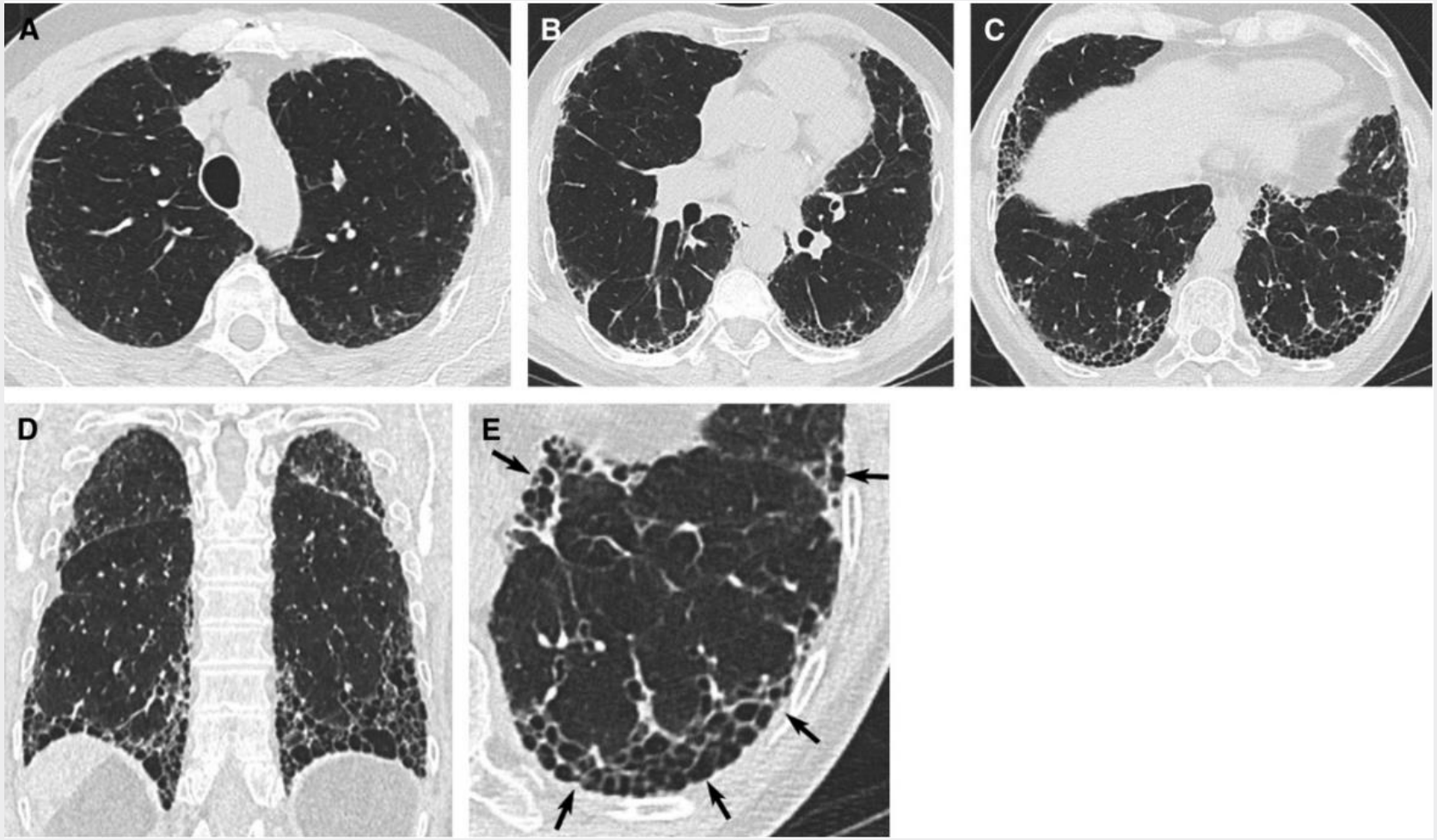


[a]Image and labeling courtesy of David A. Lynch, MD.

1. Raghu et al. *Am J Respir Crit Care Med.* 2011;183:788-824; 2. Image adapted from Mueller-Mang et al. *Radiographics*. 2007;27:595-615.

Courtesy of Dr Padilla

IPF/UIP Pattern

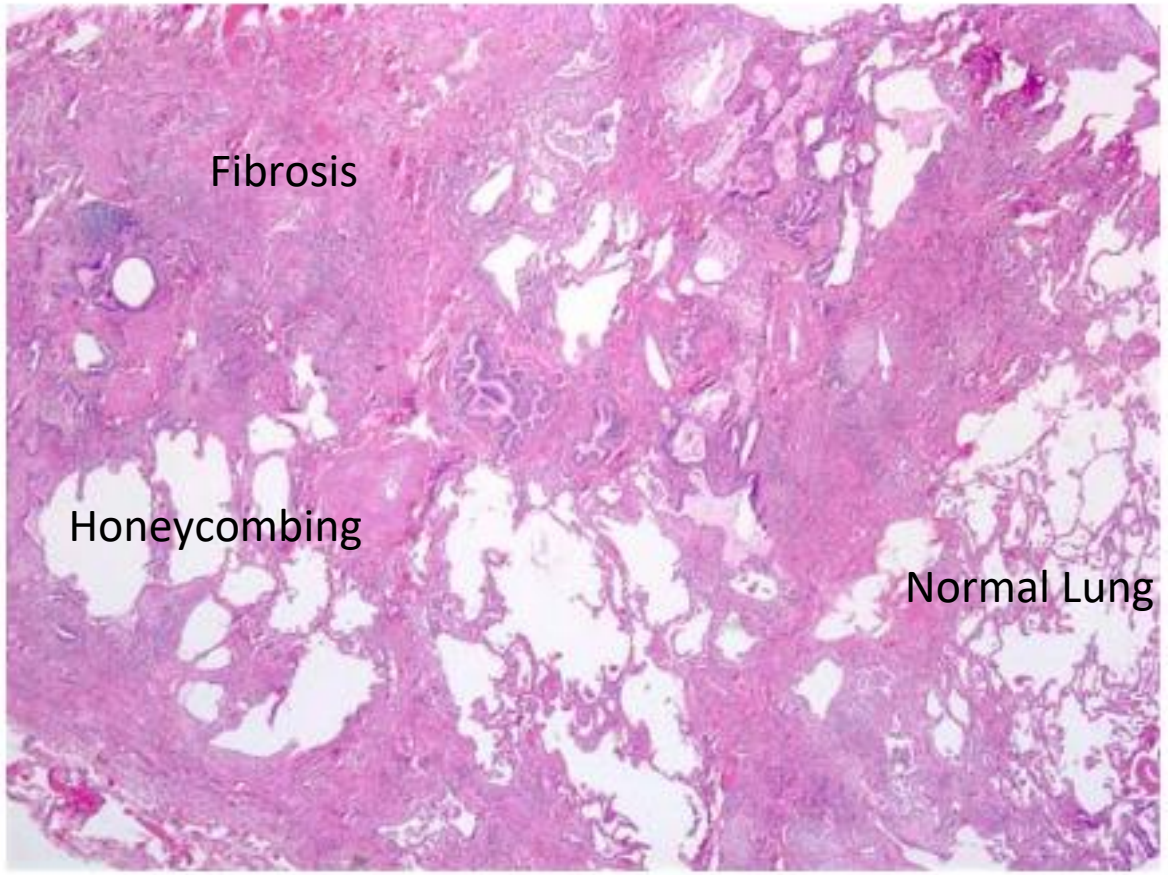


Raghu et al. Diagnosis of IPF. ATS Sep 2018

UIP Pathology

Spatial and Temporal Heterogeneity

Paucity of inflammation



Visscher et al. Histologic Spectrum of IIP. ATS. 2006

Case 1 Part C

You review imaging in your weekly multidisciplinary ILD conference and the consensus diagnosis is Probable UIP/Idiopathic Pulmonary Fibrosis. What is your next step in the management of this patient?

1. Start prednisone to help reduce inflammation
2. Start a steroid sparing agent such as cellcept
3. Start an antifibrotic
4. Refer to thoracic for a surgical lung biopsy because you are still unsure of the diagnosis
5. Refer to palliative given median survival is 2-5 years from the time of diagnosis

Case 1 Part C

You review imaging with radiology and your ILD team and consensus is this is Idiopathic Pulmonary Fibrosis. What is your next step in the management of this patient

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Approved Antifibrotic Therapies for Patients with IPF

Pirfenidone

- FDA approval 2014
- Antifibrotic properties; exact mechanism of action unknown
- Orally administered,

  801 mg, 3 times daily
- Nausea, rash/sun sensitivity, dyspepsia/GERD

Nintedanib

- FDA approval 2014
- Tyrosine kinase inhibitor; targets FGFR, PDGFR, VEGFR, FLT3
- Orally administered,

  150 mg, 2 times daily
- Diarrhea, nausea

Pirfenidone. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022535s005lbl.pdf
Nintedanib. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205832s004lbl.pdf
Galli JA, et al. *Respirology*. 2017;22:1171-1178.

Courtesy of Dr Padilla

Criteria for referral/listing for transplant

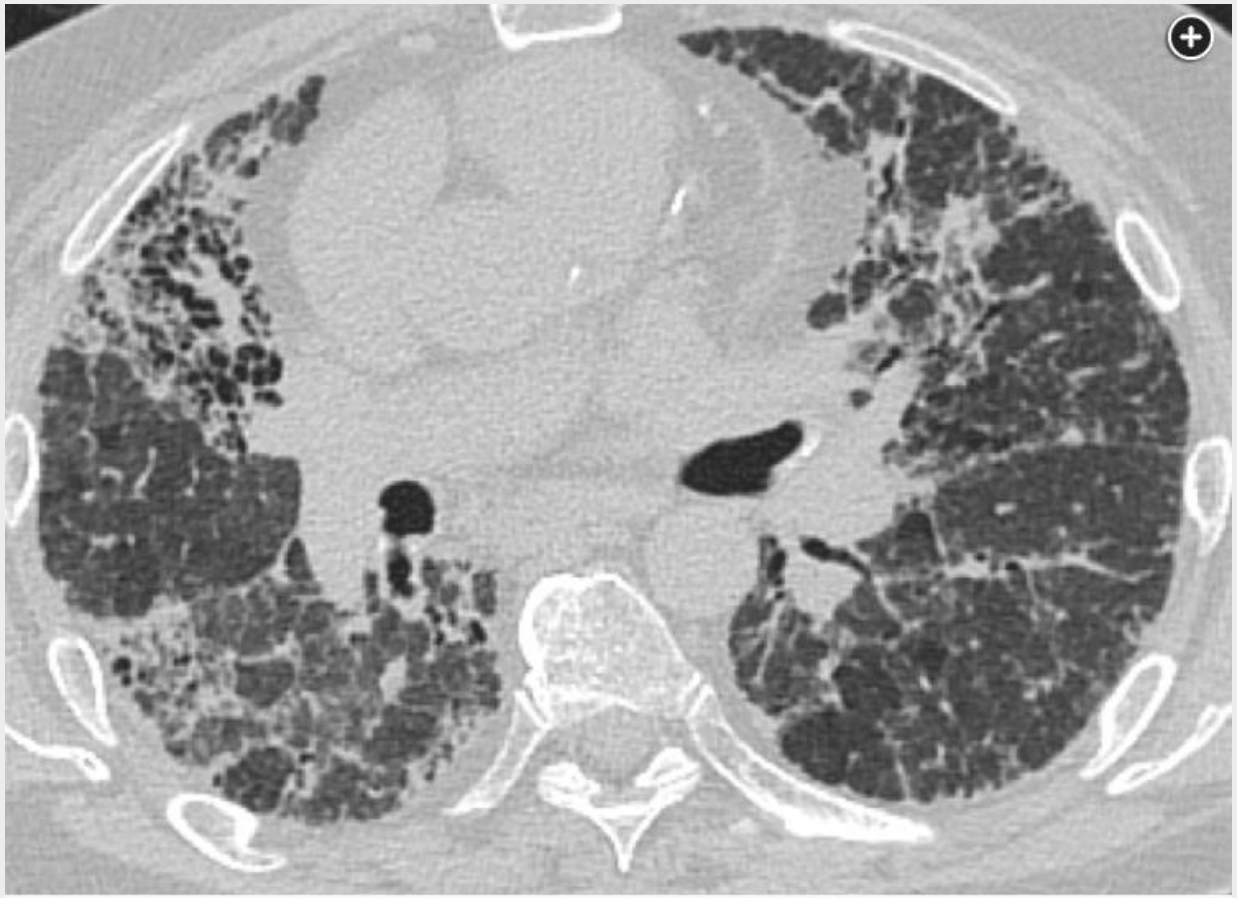
Timing of referral[#]	Timing of listing
Histopathological UIP	Hospitalisation for respiratory decline, pneumothorax or acute exacerbation
Radiographic probable or definite UIP pattern	Desaturation to <88% on 6MWT or >50 m decline in 6MWD over 6 months
FVC <80% or D_{LCO} <40% pred	Pulmonary hypertension on right heart catheterisation or echocardiography
Relative decline in pulmonary function over the past 2 years: FVC ≥10% or D_{LCO} ≥15% or FVC ≥5% with symptomatic or radiographic progression	Absolute decline in pulmonary function over the past 6 months despite appropriate treatment: FVC >10% or D_{LCO} >10% or FVC >5% with radiographic progression
Any resting or exertional oxygen requirement	
For inflammatory ILDs, disease progression despite treatment	

Kapnadak, RaghuLung Transplantation in ILD. ERR 2021 30: 210017

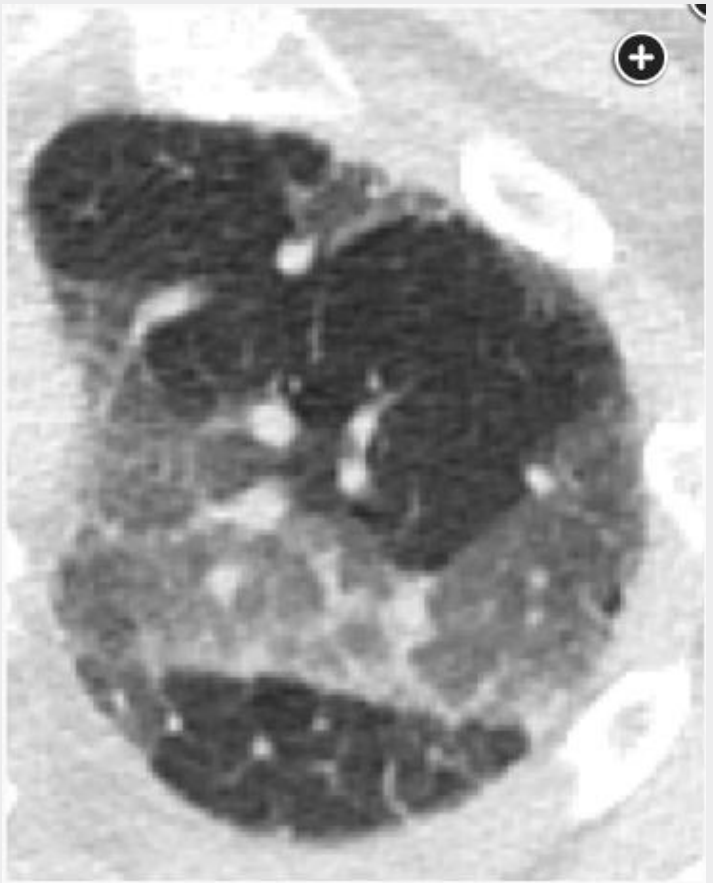
Case 2

A 45 year old woman presents with progressive dyspnea and cough over 12 months. Her medical history is notable for asthma. Medications include albuterol as needed and salmeterol/fluticasone combination inhaler twice a day. Physical examination is notable for crackles and squeaks on lung ascultation. Pulmonary function tests show the following: total lung capacity, 70% predicted; FVC, 65% predicted; FEV1, 55% predicted; and DLCO, 65% predicted. High-resolution CT chest scans are shown in Figure 1 and Figure 2. A comprehensive assessment of home and work exposures is performed and reveals the patient has a parakeet that has lived in the home for 10 years. What is the best next step in the management of this patient?

Case 2



(Figure 1)



(Figure 2)

Case 2

1. Transbronchial cryobiopsy with necrotizing granulomas
2. Serum IgG antibodies to avian antigens
3. Remove parakeet from home
4. Start prednisone

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1. Transbronchial cryobiopsy with necrotizing granulomas
2. Serum IgG antibodies to avian antigens
3. Recommend removing his parakeet from his home
4. Start prednisone

Hypersensitivity Pneumonitis

-Immune-mediated disease that manifests as ILD in **susceptible individuals** after repeated exposure to one or more inciting agents(occult or overt)

-Historically termed ”extrinsic allergic alveolitis” and previously categorized as acute, subacute or chronic

-Now categorized as **fibrotic** or **nonfibrotic** as this is the predominant determinant of prognosis

-**Exposure is not identified ~60% of patients**

-Difficult dx to make and requires MDD approach

-Heterogenous presentations, clinical course and outcomes

-Prevalence highest ~65 y/o and up

Raghu et al.Diagnosis of Hypersensitivity Pneumonitis in Adults. An official ATS/JRS/ALAT Clinical Pr

Hypersensitivity Pneumonitis

Pathogenesis:

-Protein antigen->immune reaction: both humoral (antigen-specific IgG antibodies) and T-helper 1 cell mediated immunity

-Relative switch from TH-1 to TH-2 activity, augmented epithelial apoptosis and abnormal fibroblast activity

Genetics:

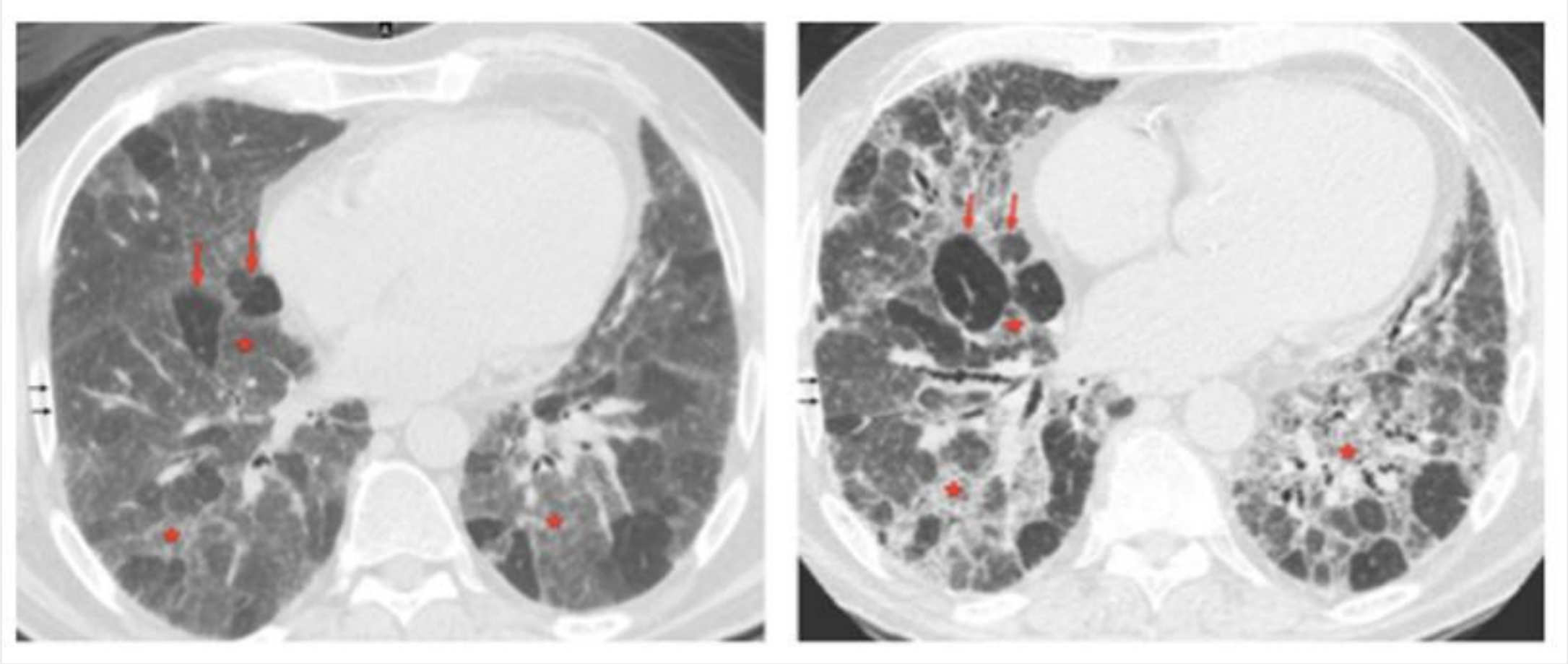
-MUC5B polymorphism and telomere-related gene mutations

Raghu et al.Diagnosis of Hypersensitivity Pneumonitis in Adults. An official ATS/JRS/ALAT Clinical Pr

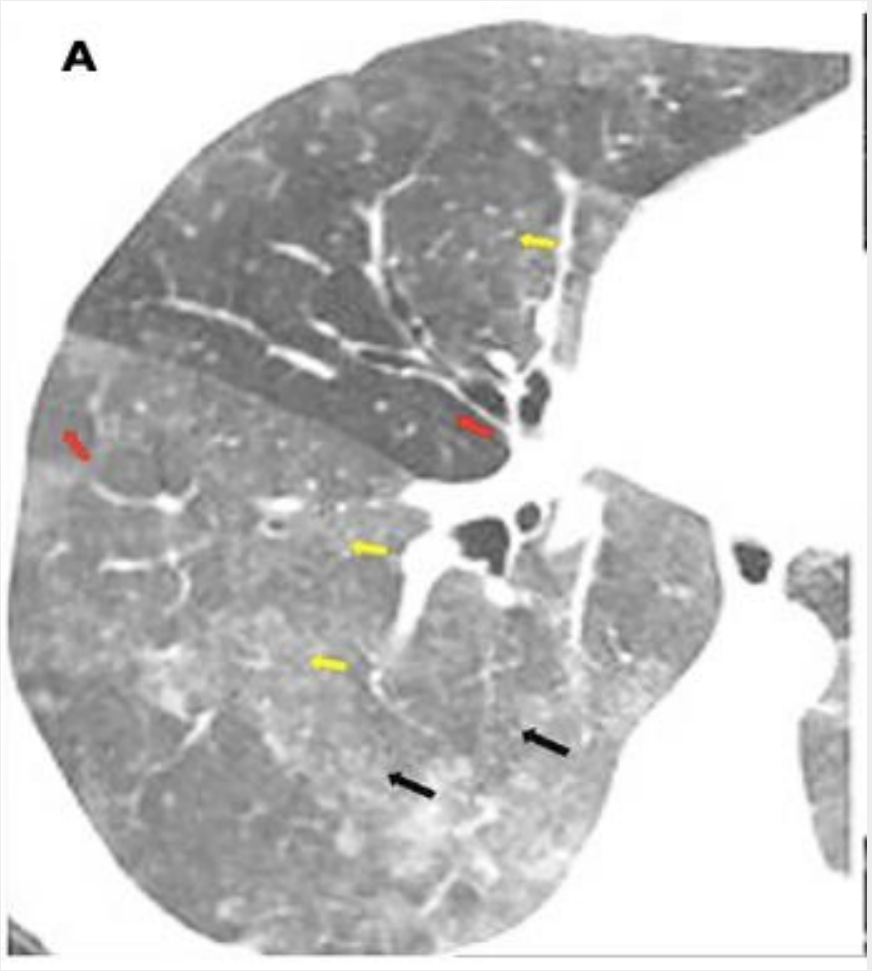
Hypersensitivity Pneumonitis

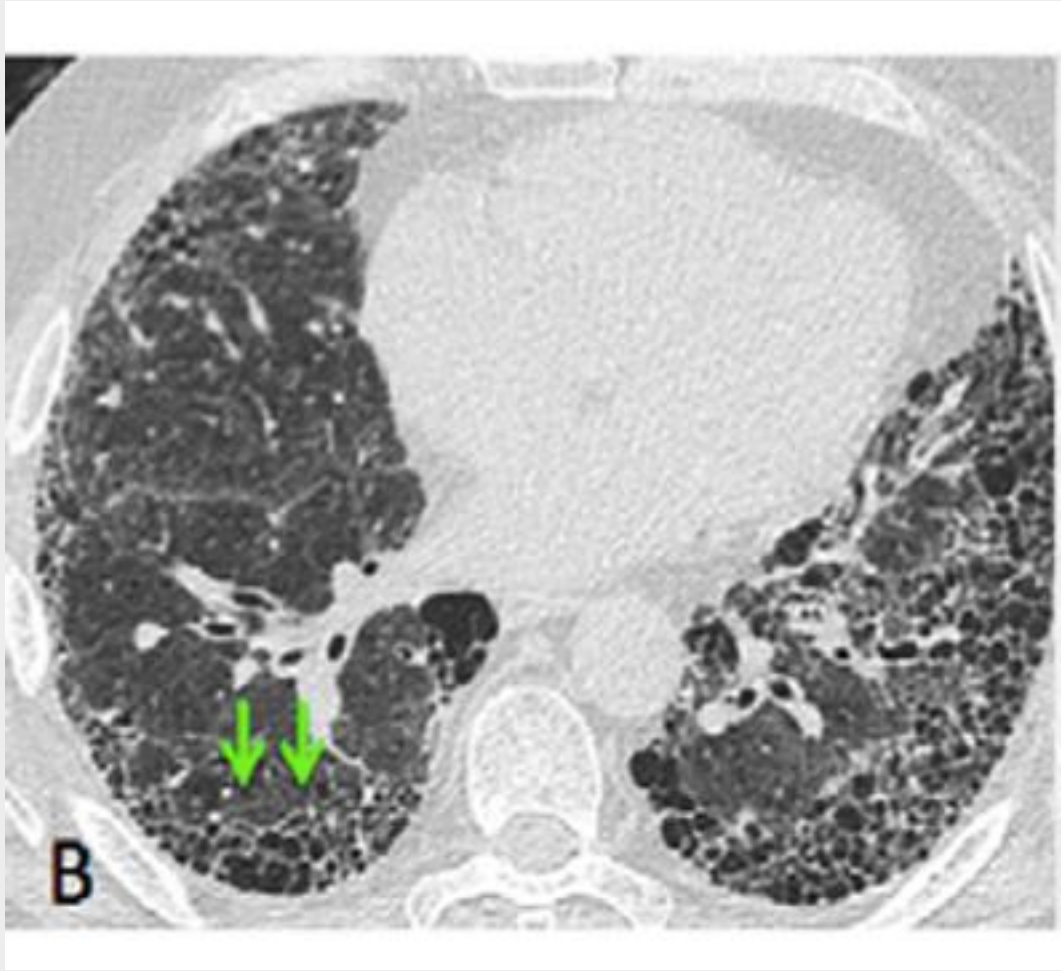
Disease	Antigen Source	Putative Antigen
Bird fancier's disease	Various birds	Protein in avian feces, feathers
Cheese worker's lung	Moldy cheese	*Penicillium* species
Coffee worker's lung	Coffee bean	Unknown
Farmer's lung	Moldy hay	Thermophilic actinomycetes
Furrier's lung	Animal fur	Protein in animal fur
Hot tub lung	Warm water	*Mycobacterium avium* complex
Humidifier lung	Warm water	Thermophilic actinomycetes
Japanese summer disease	Moldy houses	Various fungi
Machine worker's lung	Metal-cutting fluid	*Mycobacterium* species, Gram-negative bacilli
Malt worker's lung	Moldy malt	*Aspergillus* species
Mushroom worker's lung	Mushrooms	Mushroom spores, various other fungi
Peat moss worker's lung	Moldy peat moss	Various fungi
Sauna bather's lung	Sauna water	Various fungi
Sequoiosis	Moldy redwood dust	Various fungi
Suberosis	Cork	*Aspergillus* species, cork dust

Hypersensitivity Pneumonitis



Hypersensitivity Pneumonitis





Hypersensitivity Pneumonitis

Helpful diagnostics:

- Bronchoscopy: BAL lymphocytosis (30%) may be helpful in differentiating HP from IPF and sarcoid
- Transbronchial biopsy: poorly formed granulomas, lymphocytic infiltration
- Hypersensitivity panel: blood test for serum IgG to multiple antigens is not recommended because test characteristics are inferior to most screening tests used

Raghu et al.Diagnosis of Hypersensitivity Pneumonitis in Adults. An official ATS/JRS/ALAT Clinical Pr

Hypersensitivity Pneumonitis

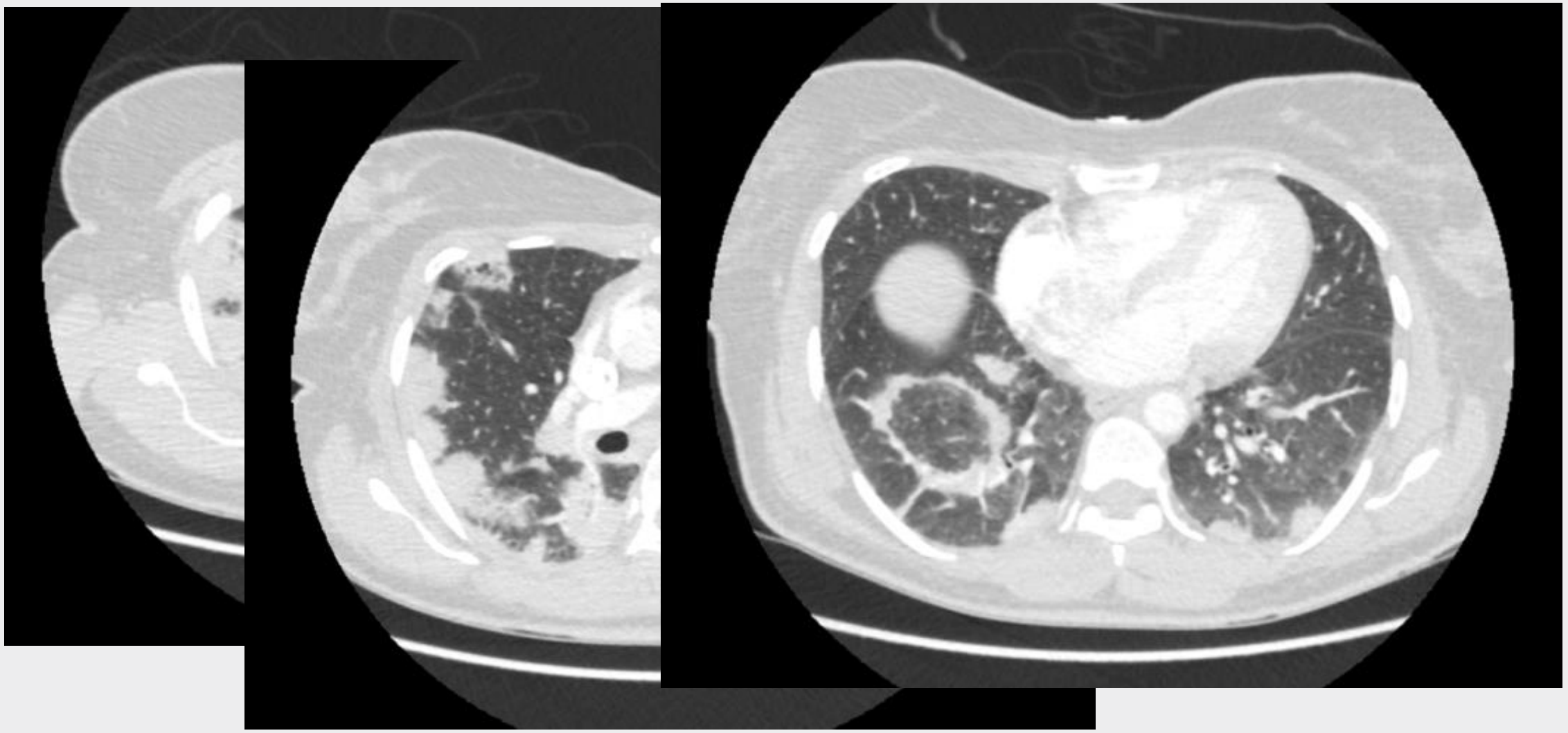
- Treatment:
  Antigen avoidance
- Corticosteroids
- Steroid sparing agents: azathioprine, mycophenolate mofetil
- Antifibrotic therapy: INBUILD study, progressive fibrosing ILD
- Lung Transplant

Raghu et al.Diagnosis of Hypersensitivity Pneumonitis in Adults. An official ATS/JRS/ALAT Clinical Pr

Case 3

A 51 year old Female with no signficant medical hx has fever, cough and dyspnea. Her symptoms began 8 weeks ago before with a flu-like illness. She initially started to feel better, but her symptoms returned, prompting her to see her PCP. She now has a productive cough of yellow sputum despite two courses of oral antibiotics. She denies hemoptysis, chest pain or GI symptoms but has lost 10 lbs since becoming ill. She never smoked and does not drink ETOH or use illicit drugs, and does not have a prior hx of recurrent respiratory tract infections. Physical examination is notable for an elevated temperature of 101.1 F with otherwise stable vital signs. oxygen saturation is 99% on 2L. Right sided crackles are noted during inspiration. Labs reveal a WBC 14,000 with an elevated neutrophil count. Sputum and fab smear are negative. Intereron-y release assay TB test is negative and HIV testing is nonreactive. A CXR reveals RUL consolidation. Chest CT images are present. BAL and bronchoscopic biopsy are nondiagnostic. Which of the following is the most likely diagnosis?

Case 3



Case 3

1. Organizing pneumonia
2. Pulmonary mucormycosis
3. Lipoid pneumonia
4. Septic pulmonary emboli

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Organizing Pneumonia

Cryptogenic organizing pneumonia (previously BOOP)

- Included in IIP because of its idiopathic nature and tendency to be confused with other IIP and pathologic features of septal infiltration by lymphoid cells with Type 2 pneumocyte hyperplasia
- Nonsmokers 2:1
- Illness is typically short, ~3 mo
- Symptoms following a LRI and patients have received 1 or more courses of antibiotics
- Weight loss, sweats, chills, fever, myalgias, productive cough
- Treatment with prolonged steroids >6 months or relapse is frequent

ATS Statement Classification of the IIP. AJRCCM Vol 165. pp277-304, 2002

Organizing Pneumonia

Table 9. CLINICAL SETTINGS ASSOCIATED WITH ORGANIZING PNEUMONIA PATTERN
As an idiopathic process that may be a localized nodule or infiltrative lung disease (COP)
Organizing diffuse alveolar damage
Organizing infections
Organization distal to obstruction
Organizing aspiration pneumonia
Organizing drug reactions, fume, and toxic exposures
Collagen vascular disease
Extrinsic allergic alveolitis/hypersensitivity pneumonitis
Eosinophilic lung disease
Inflammatory bowel disease
As a secondary reaction in chronic bronchiolitis
As a reparative reaction around other processes (including abscesses, Wegener's granulomatosis, neoplasms, and others)

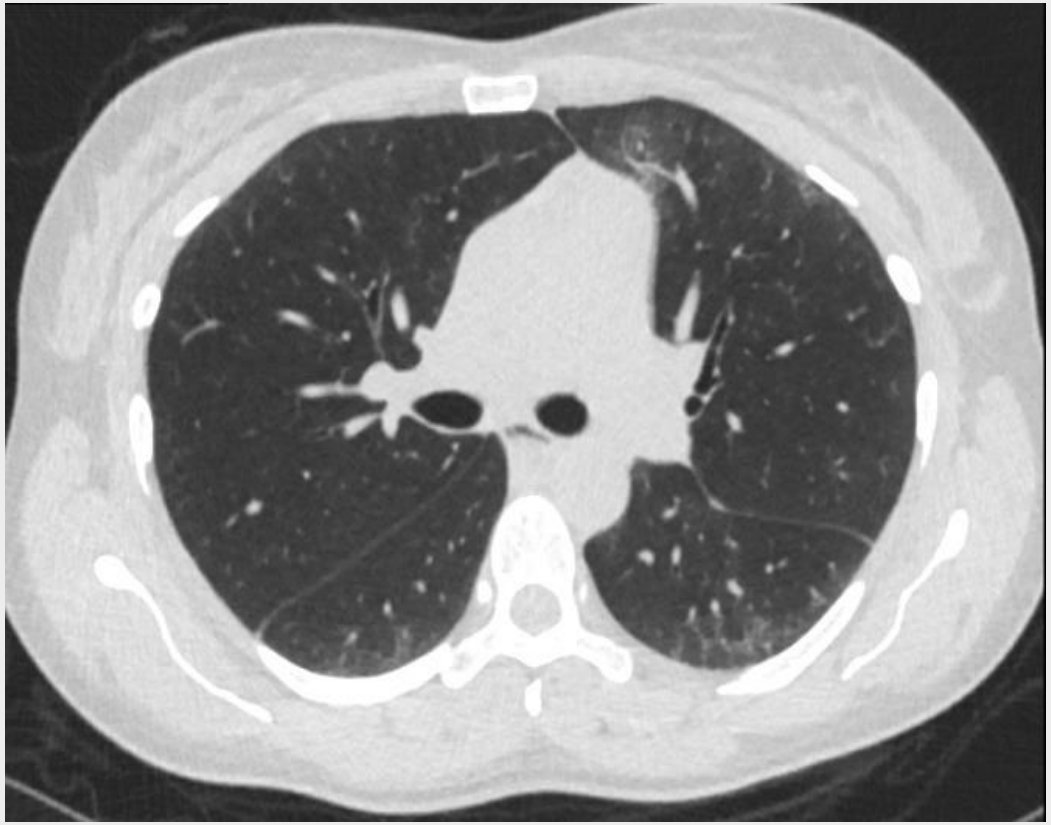
ATS Statement Classification of the IIP. AJRCCM Vol 165. pp277-304, 2002

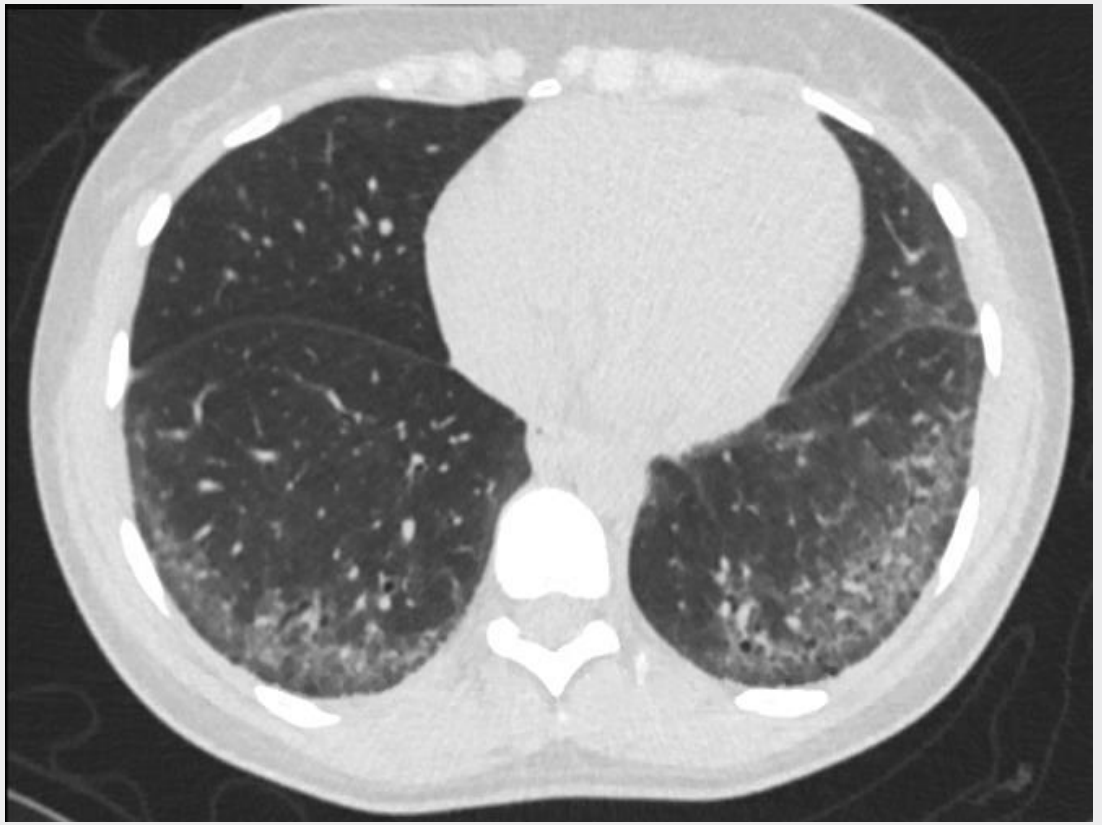
Organizing Pneumonia

- TBBx may show OP on pathology
- Pathology:
  - OP: intraluminal organizing fibrosis in distal air spaces (bronchioles, alveolar ducts and alveoli), patchy distribution, preservation of lung architecture, uniform temporal appearance, mild interstitial chronic inflammation
- Radiographic findings:
  - Unilateral/bilateral consolidative opacities, patchy, subpleural or peribronchial, lower lobe predominant, air bronchograms; migratory infiltrates

Case 4

41 year old female presents with dyspnea





Case 4

Physical Exam:

- HEENT: restricted oral aperture, loss of wrinkling of the forehead
- RESP: bibasilar velcro crackles
- MSK: sclerodactaly
- SKIN: thickened skin over the distal digits to the wrists, also on the forearms and dorsal feet, but the trunk and proximal extremities have normal skin texture, Few scattered dilated nailfold capillaries. There are firm (bony) subcutaneous nodules on the right

Case 4

Labs:

- **Laboratory Studies:**
- **Results** **Normal Values**
- ANA 1:1280 with a homogeneous pattern (<1:40)
- Anti-RNA III 20 U (<19 U)
- Anti-Scl 70 131 AU/ml (<29 AU/ml)

Case 4

What is your diagnosis?

1. mixed connective tissue disease ILD
2. unspecified autoimmune disease associated ILD
3. SLE associated ILD
4. Scleroderma associated ILD

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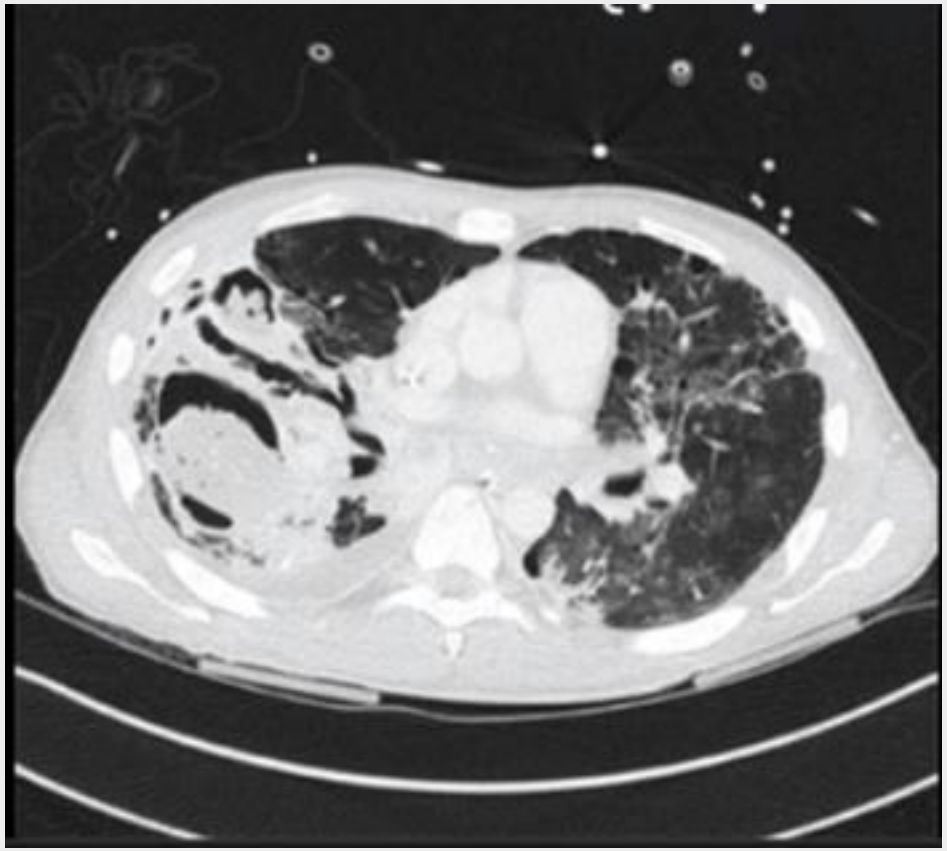
1. mixed connective tissue disease ILD
2. unspecified autoimmune disease associated ILD
3. SLE associated ILD
4. Scleroderma associated ILD

Scleroderma-ILD

- Complex autoimmune disease characterized by small-vessel vasculopathy and multi-system fibrosis of the skin, GI tract and respiratory system
- Most common autoimmune disease associated with ILD
- Diffuse scleroderma more likely to develop ILD
- Anti-SCl-70/anti-topoisomerase I antibody associated with ILD
- Anti-RNA polymerase III is highly specific for scleroderma and is associated with rapidly progressive diffuse skin thickening and scleroderma renal crisis
- Treatment with steroid sparing agents
- First line: mycophenolate (steroids can precipitate scleroderma renal crisis)

Case 5

A 50 year old african american woman presents for hemoptysis. She has a CTA chest performed which can be seen below. What is the most likely cause of her underlying lung disease?



Case 5

1. Cystic Fibrosis
2. Pulmonary Tuberculosis
3. Chronic Hypersensitivity Pneumonitis
4. Pulmonary Sarcoidosis

Case 5

1. Cystic Fibrosis
2. Pulmonary Tuberculosis
3. Chronic Hypersensitivity Pneumonitis
4. Pulmonary Sarcoidosis

Sarcoidosis

- Multi-system inflammatory disease commonly affecting the respiratory system
- ~20% develop fibrotic lung disease due to an exuberant fibrotic response
- Pathophys: T-cell mediated response to an unidentified antigen->cytokine release->granulomas
- Granulomatous inflammation occurs primary along the lymphatics
- Fibrotic sarcoidosis=“burnt-out” disease-absent granulomatous inflammation and treatment is unhelpful
- Upper and middle lobe predominant, with highly variable patterns with a lymphatic distribution
- Wheezing due to airway centered fibrosis
- Mixed obstruction and restriction on pfts

Patterson and Strek. Pulmonary Fibrosis in Sarcoidosis. ATS August 2013.

Sarcoidosis

Treatment

- Does immunosuppression prevent fibrosis? no…
- Some may have concomitant inflammation and fibrosis-hard to determine those that may benefit from immunosuppression

Table 3. Considerations in initiating therapy in fibrotic pulmonary sarcoidosis

Clinical features favoring active pulmonary sarcoidosis
Subacute onset of pulmonary symptoms
Persistence of symptoms
Elevated ACE level; insensitive but can be helpful when levels track with disease activity
Less-specific clinical features of active sarcoidosis
Fevers, night sweats, or weight loss; evaluate for infection or malignancy in patients with a long period of inactive sarcoidosis
Elevated CRP or ESR; if substantially elevated consider alternative diagnoses
Thoracic lymphadenopathy; may not reflect active disease if unchanged from prior imaging
Conditions to exclude
Systolic and diastolic cardiac dysfunction
Pneumonia, upper respiratory tract infection, or exacerbation of bronchiectasis
Asthma
Pulmonary embolism
Pulmonary hypertension

Patterson and Strek. Pulmonary Fibrosis in Sarcoidosis. ATS August 2013.

Thank you! Questions?

stephanie.iusim@bannerhealth.com