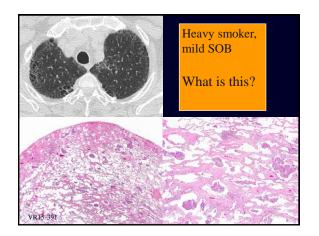
Smoking-Related Interstitial Lung Disease: New Ideas, Entities, and Nomenclature

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Conflicts of Interest

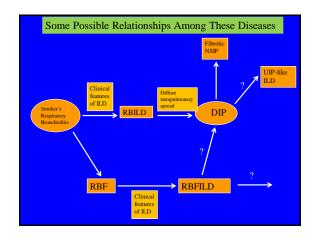
• I have no conflicts of interest to disclose

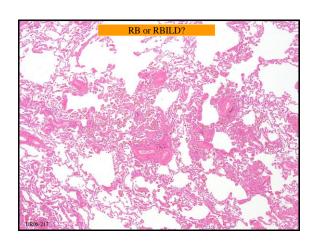


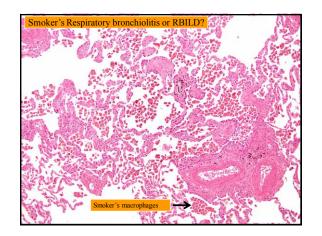
Interstitial Lung Disease Caused by Smoking

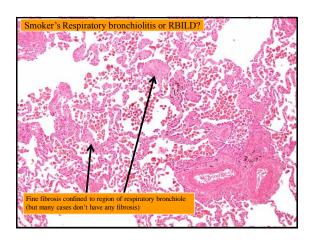
Clinical/Radiologic/Pathologic Entities

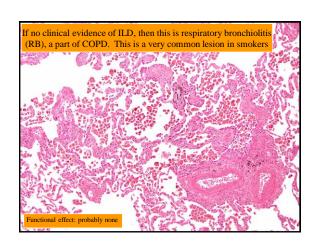
- Probably usual interstitial pneumonia (UIP)
 - 70% of UIP patients are current or former smokers
- Combined pulmonary fibrosis with emphysema (CPFE)
- Langerhans cell histiocytosis (LCH)
- Desquamative interstitial pneumonia (DIP)
- Respiratory bronchiolitis with interstitial lung disease (RBILD)
- Respiratory bronchiolitis with fibrosis-interstitial lung disease (RBFILD)
 - Also called smoking-related interstitial fibrosis, airspace enlargement with fibrosis, RBILD with fibrosis

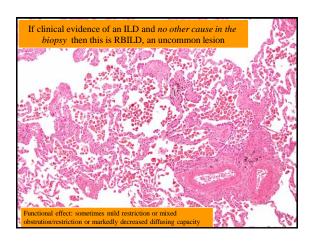




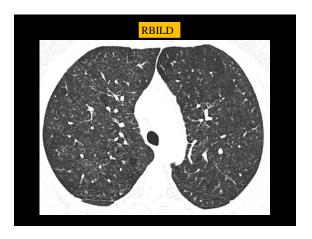












"Smoking-Related Interstitial Fibrosis" as a Specific Pathologic Entity: Nomenclature

- Yousem 2006: "Respiratory bronchiolitis-associated interstitial lung disease with fibrosis" (RBILDF)
- Kawabata 2008: "Airspace enlargement with fibrosis" (AEF)
- Katzenstein 2010/2012: "Smoking-related interstitial fibrosis" (SRIF)
- Reddy 2013: "Respiratory bronchiolitis with fibrosis (RBF/RBFILD)" [pathologic and radiologic definition]
- Flaherty 2014: "Smoking-related idiopathic interstitial pneumonia" [clinical/radiologic definition]
- NB: RBILDF, SRIF, AEF, RBF are *mostly* all the same thing

Respiratory Bronchiolitis with Fibrosis (RBF): Prevalence

- · Limited data but the lesion is probably fairly common:
- Yousem 2006: 9/32 cases originally called 'nonspecific interstitial pneumonia' (NSIP)
 - Also found in a milder form in 4/30 lung cancer lobectomies
- Kawabata 2008: 21% of lungs from heavy smokers, mostly lower lobe
- Katzenstein 2010/2012: 9/20 (45%) of extensively sampled smoker's lungs, always in upper and middle zones
- C English 2014: 7% of heavy smokers in a large HRCT survey
- Flaherty 2014: 8% of heavy smokers (HRCT)

RBF: Clinical Features

- · Yousem:
 - Shortness of breath/dry cough
 - Age range 32-68 (avg 44), avg smoking: 38 pack-years
 - 4 patients had mixed obstructive/restrictive defect
- Katzenstein
 - Lung cancer resections age range 52-77, avg smoking 36 pack-years
 - Most patients had airflow obstruction (COPD)
- Kawabata: Lung cancer resections
 - No data on functional changes or imaging
 - Many were heavy smokers
- Reddy:
 - Heavy smokers (avg 53 pack-years), shortness of breath
 - Mild airflow obstruction/markedly decreased diffusing capacity
- C English: smokers with >30 pack-years (avg 56±19)
 FEV₁ (Mean, SD): 81±10% predicted; FEV₁/FVC 73±6%

Examples of PFT Changes in RBF*

From Reddy et al 2013

64%

59%

•	Case 1	Case 6	Case
• FEV ₁	63%	62%	89%
• FVC	69%	62%	1029
• FEV ₁ /FVC	72%	68%	69%
• TLC	98%	93%	93%

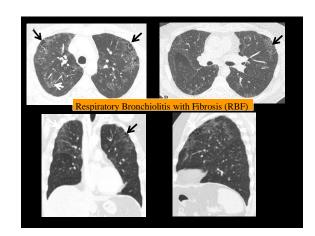
56%

• *as % predicted, except FEV₁/FVC

• DL_{co}

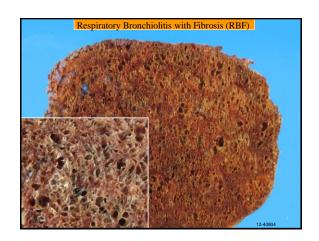
RBF: Radiologic Features

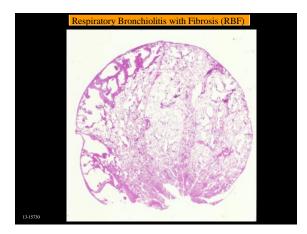
- Reddy et al 2013:
 - Distinctly circumscribed upper / mid zone patches of reticulation surrounding paraseptal/centrilobular emphysema
 - Reticulation absent or minimal in the lower zones
 - Ground glass opacities often present
- C English et al 2014
 - 79% both upper lobes
 - 21% one upper lobe
 - 43% superior segment lower lobe
 - · No basal disease

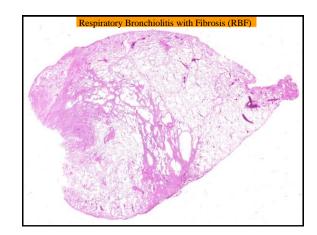


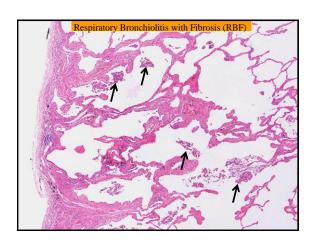
RBF: Pathologic Features

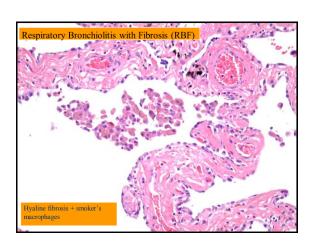
- Localized patches of interstitial fibrosis
- Fibrotic area often wedge-shaped, radiating from respiratory bronchiole to pleura
- Fibrosis typically hyaline
- Fibrosis admixed with emphysema
- Smoker's macrophages always present, sometimes in large numbers
 - Can locally mimic desquamative interstitial pneumonia (DIP)
- No honeycombing
- Fibroblast foci rare to absent (not seen by us, not described by Yousem, occasional fibroblast foci described by Katzenstein and by Kawabata)

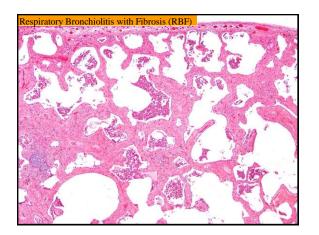


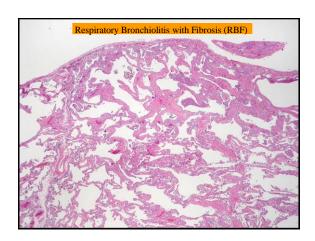


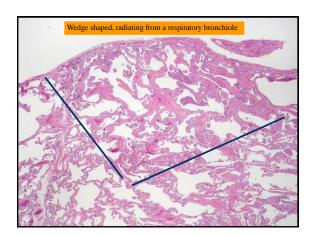






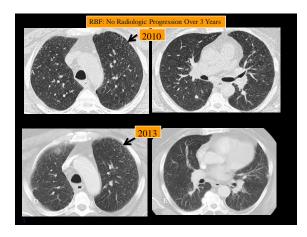


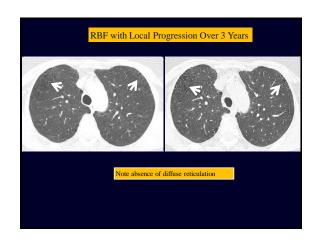


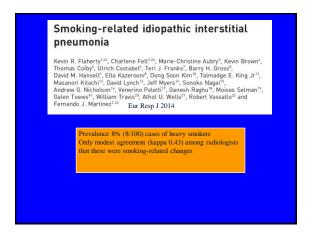


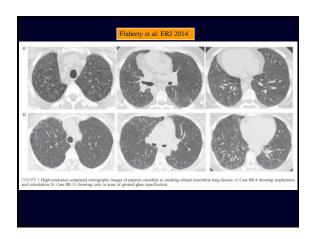
Prognosis of SRIF/RBF

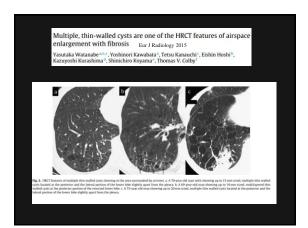
- Katzenstein 2010: Patients stable vis a vis SRIF (1 cancer recurrence)
- Yousem:
 - Mean followup 3.2yr
 - 7/9 stable disease
 - 2/9 slowly progressive disease
 - Two cases had progression of COPD but not of ILD (Yousem, personal communication)
- Reddy: 3 patients with followup stable
- C English:
 - Mild local radiologic progression in 14% over 2.6 years, but no progression to diffuse fibrotic disease (86% radiologically stable)











Why Worry About RBF?

- Frequently mistaken for a diffuse fibrosing ILD
 - Referring diagnoses in the Reddy series:
 - ILD not yet diagnosed
 - ILD not yet diagnosed
 - Incidental finding, ? ILD
 - ? Chronic HP/? Sarcoid
 - ? Pneumoconiosis
 - Sometimes called honeycombing on HRCT
- Some patients have a mild ILD (RBFILD, analogous to RBILD)

What's the Difference Between RB vs RBILD and RBF vs RBFILD?

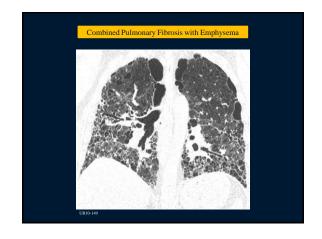
- RB and RBF are essentially incidental (but sometimes morphologically dramatic) findings
- RBILD and RBFILD require a *clinical decision* that the patient has an interstitial lung disease
 - More extensive GGOs than one sees in RBILD
 - Reticulation with emphyema
 - Restrictive PFT
 - Disproportionately reduced diffusing capacity
- RBILD and RBFILD cannot be diagnosed on biopsy alone

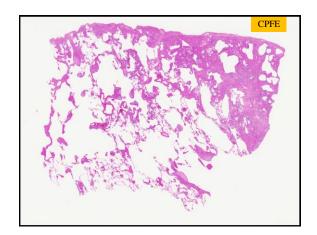
Pathologic/Clinical Entities and Functional Effects

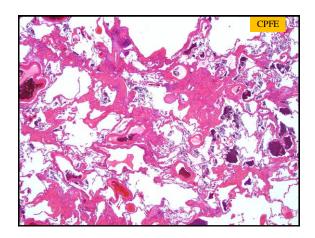
- Probably No Effect (usual scenario)
- Respiratory bronchiolitis (RB)
- Respiratory bronchiolitis with fibrosis (RBF)
- Mild ILD (uncommon scenario)
- Respiratory bronchiolitis with interstitial lung disease (RBILD)
- RBF with interstitial lung disease (RBF-ILD)

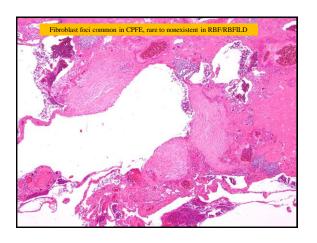
Differential Diagnosis of RBF/RBFILD

- Combined pulmonary fibrosis and emphysema (CPFE)
 - All cases show diffuse fibrosis
 - Radiologically most commonly looks like UIP with basal fibrosis/honeycombing and upper zone emphysema
 - Microscopically mixture of extensive architecturally distorting fibrosis and emphysema
- Desquamative interstitial pneumonia





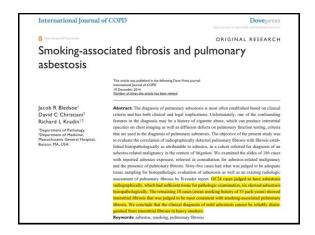


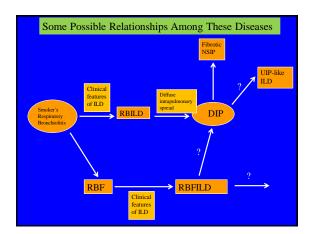


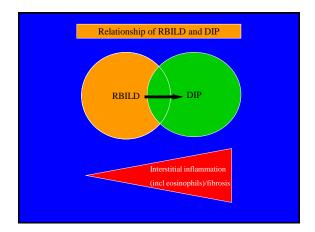
Nomenclature Choices Mild Interstitial Lung Disease RBILD with fibrosis (Yousem) Smoking-related interstitial fibrosis (SRIF) (Katzenstein) Respiratory bronchiolitis with fibrosis (RBF) (Reddy) Respiratory bronchiolitis with fibrosis-ILD (RBFILD) Not defined (Flaherty) Smoking-related idiopathic interstitial pneumonia (SIIP)

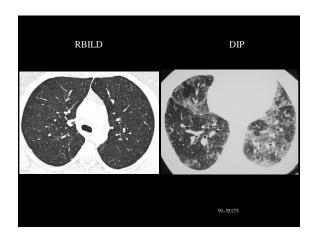
Conclusions re RBF

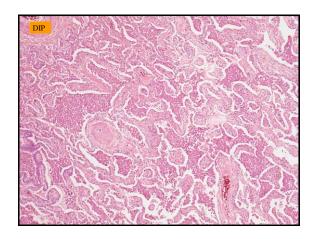
- There is a specific morphologic entity of RBF: respiratory bronchiolitis with fibrosis
- · It is associated with heavy smoking
- It can be detected radiologically in some cases (then = RBFILD)
- Most patients with only pathologic RBF probably have no functional consequences, but, by analogy with RB/RBILD, some patients have a mild ILD (RBFILD)
- RBF/RBFILD is frequently mistaken pathologically and radiologically for a diffuse fibrosing interstitial pneumonia

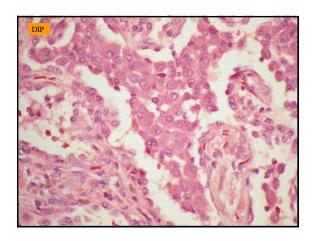


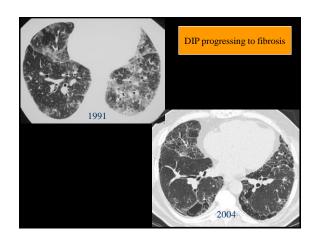


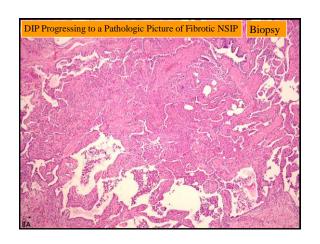


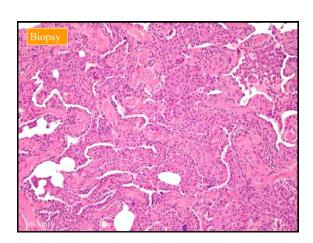


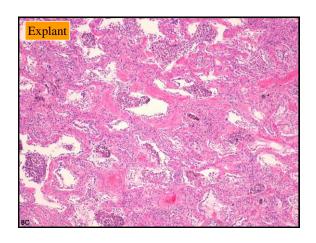


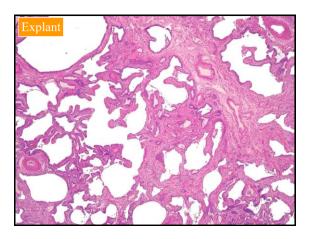




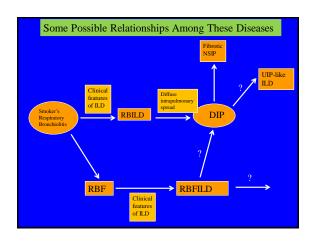


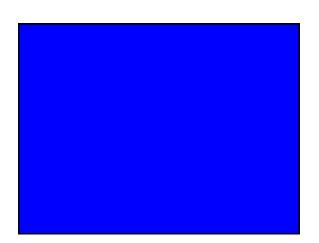


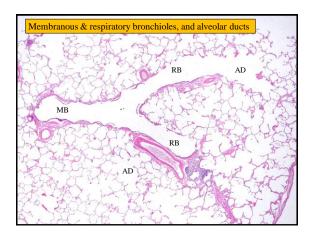




Treatment/Survival in RBILD/DIP · Treatments: Steroids, smoking cessation Outcomes RBILD DIP (% survival) • Carrington 78 ND 72% (9 yrs) • Yousem 89 100% 68% • Ryu 05 100% 74% • Portnov 07 96%* • Kawabata 12 78% (10 yrs)** **Only 1 DOD but 36% honeycombing





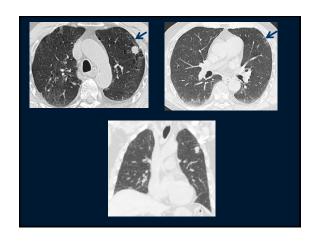


Smoking and COPD

- Most cigarette smokers develop COPD (chronic obstructive lung disease)
 - Functional defect: airflow obstruction
- Radiologic and pathologic manifestations
 - Emphysema
 - Small airway remodeling
 - Smoker's respiratory bronchiolitis
- None of these lesions are "interstitial"

Interstitial Lung Disease Caused by Smoking

- Prevalence: 8 to 15% of smokers in large radiologic surveys (Washko 2011; Lederer 2009; Sverzellati 2011)
- Some patients have a restrictive functional defect and/or
- Disproportionately decreased diffusing capacity
- This can also be seen with severe COPD
- CT changes
- Reticulation (implies underlying fibrosis)
- Traction bronchiectasis/bronchioectasis (implies underlying fibrosis)
- Honeycombing
- Ground glass opacities
- In these types of surveys, pathologic lesions that =
 "interstitial lung disease" caused by smoking largely
 undefined



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- Flaherty 2014: "Smoking-related idiopathic interstitial pneumonia" [clinical/radiologic definition]
- "Smoking related interstitial fibrosis" is the most logical name, but that term tends to get used casually for any kind of smoking-related ILD