



# Dyspnea: A Rheum with a View

Jennifer Green Brackney, DO, FACOI

# Our Patient continued

- 56 yo female with history of seropositive RA for greater than 10 years
- DM, HTN, hypercholesterolemia, obesity
- 1 week history of worsening dyspnea
- Stable on the following meds:
  - methotrexate 10 mg PO weekly (4 – 2.5mg tablets one day a week)
  - folic acid 1 mg daily
  - enbrel (etanercept) 50 mg SQ weekly
  - IBP 800 mg daily PRN only
- FHx: mother with type 2 diabetes & younger brother with asthma
- Patient smokes 1/2 ppd x 40 years
- No travel history

# Ddx Dyspnea

- Acute:
  - Asthma, pneumonia, pulmonary edema, PTX, PE, metabolic acidosis, ARDS, panic attack
- Pulmonary
  - Airflow obstruction (asthma, COPD, upper airway obstruction)
  - Restrictive lung disease (ILD, pleural thickening or effusion, respiratory muscle weakness, obesity)
  - Pneumonia
  - Pneumothorax
  - Pulmonary embolism
  - Aspiration
  - ARDS
- Cardiac:
  - MI, CHF, valvular obstruction, arrhythmia, cardiac tamponade
- Metabolic
  - Acidosis, hypercapnia, sepsis
- Hematologic
  - Anemia, methemoglobinemia
- Psychiatric
  - Anxiety

# What's different?

- What's different about the approach to dyspnea in a rheum patient?
  - Disease sequelae
  - Medications
    - Toxicity - Drug-related lung disease 2<sup>o</sup> drugs used to tx RA
    - Immunosuppression - Infection 2<sup>o</sup> immunosuppression
  - Overlapping clinical syndromes

# Respiratory Disease in RA

## Interstitial

- Interstitial pneumonitis/fibrosis (RA-ILD)
  - Usual interstitial pneumonia (UIP)
  - Nonspecific interstitial pneumonia (NSIP)
  - Organizing pneumonia
  - Lymphocytic interstitial pneumonia (LIP)
  - Desquamative interstitial pneumonia (DIP)
- Bronchiolitis obliterans with organizing pneumonia
- Rheumatoid nodules
- Rheumatoid pneumoconiosis (Caplan's syndrome)
- Apical fibrobullous disease

## Pleural

- Pleuritis
- Pleural effusion
- Pleural thickening
- Chyliform effusion

## Airway

- Cricoarytenoid arthritis/central airway obstruction
- Obliterative bronchiolitis
- Bronchiectasis
- Bronchiolitis obliterans with organizing pneumonia
- Chronic small airway obstruction

## Chest Wall

- Thoracic cage immobility

## Pulmonary vascular

- Pulmonary hypertension
- Vasculitis

## Other

- Infection
- Drug-related
- ? Lung cancer

# Serologies

- **CBC**
  - WBCs ?infection
  - Hb ?anemia
- **CMP**
  - Cr ?pulm-renal syndrome
- **RF**
  - Not useful in a pt with established RA as it yields no information about RA disease activity or the cause of the dyspnea

# The Diagnostic and Prognostic Significance of Autoantibodies in Very Early RA

- Purpose: to determine the sensitivity, specificity and positive predictive value of RF, anti-CCP, and anti-A2/RA33 in differentiating RA from other arthropathies in very early arthritis

	RA (n=100)	non-RA (n=80)	Sensitivity %	Specificity %	PPV %
RF ≥20	54	9	54	89.0	85.7
RF ≥50	46	2	46	97.4	95.8
Anti-CCP	38	1	38	98.7	97.4
Anti-A2/RA33	26	8	26	90.0	76.4
RF ≥20 pos + anti-CCP pos	30	0	30	100.0	100.0
RF ≥20 pos + RA33 pos	15	0	15	100.0	100.0
RF ≥20 neg + anti-CCP pos	8	1	8	98.7	88.9

Nell VPK, et al. ACR 2003, #167

Anti-CCP and RF ≥50 have a PPV of 78% and 88% for developing erosive disease

# Positive correlation of extra-articular RA with anti-CCP antibody

- **Anti-CCP positivity associated with:**
  - Nodules
  - Lung disease
  - Scleritis
  - Sjogren's syndrome
- **Diabetes and RA - RF and CCP positivity associated with:**
  - Higher prevalence of extra-articular RA
  - Association with advanced glycosolated end products (AGE)

# RA

- RA is a common **systemic** inflammatory disease affecting approx 1-2% of the general population
  - characterized by chronic symmetrical erosive synovitis
- Nearly 50% of pts with RA will demonstrate extra-articular manifestations
- Nonarticular manifestations of RA include SQ nodules, vasculitis, pericarditis, mononeuritis multiplex, episcleritis and lung disease
- Pulmonary and pleural abnormalities are common in patients with RA, but may not result in significant symptoms

# History of RA Lung Disease

- Ellman and Ball published the first clinical report of pulmonary involvement in RA in 1948
- 1953 Caplan described the now classic trio of rheumatoid lung nodules of coal miners suffering RA
- 1955 Sinclair and Cruikshank postmortem findings of pleural disease twice the rate of normal population
- 1961 Culkowicz et al reported the first case of “rheumatoid lung”

# Pneumonitis

- Unlike pulm rheumatoid nodules, the severity and progression of interstitial pneumonitis does not necessarily correlate with severity of joint disease
- Risk factors: smoking, male sex, presence of other extra-articular findings
- Diffuse pneumonitis in the setting of DMARDs in RA patients presents a broad ddx
  - CAP, sepsis/ARDS, CHF, oliguric renal failure, accelerated phase of usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), acute interstitial pneumonia, drug reaction, hypersensitivity pneumonitis
  - The last 3 occur in increased frequency in RA pts

# Interstitial fibrosis

- Most common diffuse pulm involvement caused by CTD
- Most freq found in scleroderma and RA
- 90% of RA pts affected, jt dz precedes lung dz
- Clinical presentation, pathology, disease spectrum, and pathogenesis of RA-ILD is similar to that of the idiopathic interstitial pneumonias (IIPs)
- Pulm-fibrosis assoc RA more common in men btw 50-60 y/o with seropositive nodular dz
- Radiographically, changes usu occur periph, sub-pleural. Reticular, reticulonodular or honeycomb pattern.
- GGOs on HRCT = active alveolitis → fibrosis as dz progresses with increased thickening of the interstitium causing reticular pattern on HRCT → coarse scars & cystic spaces result in honeycombing
- Histologically, the abnormalities are highly variable but usually resemble one of the IIPs
- PFTs restrictive with dec lung volume, inc FEV<sub>1</sub>/VC & dec DLCO after adjustment for Hb

# Pleural

- One of the most common manifestation of lung disease in RA, but it is usually subclinical
  - 40% of post-mortem cases, but only 5-20% have symptoms due to pleural involvement
- Most common in pts with longstanding RA, more common in men and coexists with nodules and ILD in up to 30% of pts
- Pleural effusions frequently occur during periods of active arthritis
  - A few develop effusions before arthritis
  - May also lead to PTX & empyema
  - Can be caused by necrosis and cavitation of a nodule into the pleural space
- S/s of chest pain and/or fever are most common, dyspnea if significant pleural effusions

# Bronchiolitis obliterans

- Organizing pneumonia (OP), also known as bronchiolitis obliterans organizing pneumonia (BOOP) or cryptogenic organizing pneumonitis (COP) is a proliferative bronchiolitis
- Inflam of bronchioles & alveolar ducts leads to plugging by granular tissue → obliteration by fibrosis
- In RA, historically assoc with penicillamine tx, but may occur without its use
- Pts present with cough, dyspnea, malaise, weight loss, and fever. Crackles are noted on PE
- Lab & XR reveals:
  - ESR usually elevated.
  - CXR: bilat parenchymal opacities, often with preserved lung volumes
  - Lung physiology demonstrates a restrictive picture, with a decDLCO and hypoxemia
  - HRCT shows unilateral or bilateral consolidation that is patchy and often peripheral
- Dx made lung biopsy - demonstrates patchy intraluminal polypoid plugs of immature fibroblast tissue within respiratory bronchioles

# Pulmonary complications from drugs used to tx RA

- **Pneumonitis**
  - MTX, Gold, Leflunomide, d-Penicillamine, NSAID, Cyclophosphamide (CYC), Azathioprine (AZA), Sulfasalazine (SSZ)
- **Fibrosis**
  - MTX, Gold, CYC, AZA, SSZ
- **Bronchiolitis obliterans**
  - D-Pen, Gold, SSZ
- **Infection**
  - TNF's, MTX, Glucocorticoids, CYC
- **Noncardiac pulmonary edema**
  - High dose aspirin, NSAID, MTX,

# Medication related injury

- **Methotrexate**
  - Life threatening acute pneumonitis is the most feared
  - 0.3-11.6% of RA pts within the first 6 mos
  - Sxs nonspecific: dry cough, dyspnea
  - HRCT patchy GGOs with centrilobular nodules, LAD
  - Mortality 15% in a recent series
- **Leflunomide (Arava)**
  - Diffuse pneumonitis is an uncommon reaction to leflunomide
    - < 0.1% of treated pts
  - Likely to occur early in course of tx
  - May be more common in those of East Asian ancestry
- Elevated CD4/CD8 ratios in BAL fluid of drug-induced ILD may be helpful in differentiating from other causes of ILD

# Medication related injury

- **D-Penicillimane**
  - Most often used in the treatment of scleroderma, can cause an obliterative bronchiolitis
- **Gold**
  - Consolidation & fibrosis
- **Anti-TNFs**
  - > 20 cases of sarcoid-like granulomatous disease in RA pts
  - Evolves between 1 month & 5 years
  - Resolves with discontinuation of tx

# Infection

- Pulm infection in RA pts patients usu results in higher morbidity and mortality
- PNA, bronchiectasis, empyema, & infected nodules.
- Suspected predisposing factors for pulmonary infections include:
  - Underlying lung disease
  - Host defense abnormalities (eg, poorly defined lymphocyte abnormalities)
  - Immunosuppressive drugs
- S/s of infection can be altered, since fever and leukocytosis may not be present because of immunosuppressive tx

# Infection

- Mycobacterium
  - M. Tb & atypical
- Histoplasmosis
- Listeriosis
- Aspergillosis
- Pneumocystis
- Nocardia
- CMV
- Chlamydia
- Legionella
- Note:
  - All pts who are being considered for TNF inhibitor **must** undergo PPD testing
  - All RA pts should be immunized annually against influenza and pneumococcal vaccination every 5 years
- Pts on MTX have been shown to have a suboptimal response to vaccinations
- Live vaccination is contraindicated in pts on TNFs

# RA and CV disease

- 30% of RA pts have echo evidence of valve thickening or incompetence
- ~50% of RA pts have evidence of pericardial involvement
- RA & accelerated atherosclerosis
  - Is it the disease?
    - Inflammation promotes atherogenesis
  - Is it the treatment?
    - NSAID's or COX-2 inhibitors
    - Corticosteroids
- Target modifiable risk factors
  - LDL
  - Tobacco

# Vasculitis

- Well recognized extra-articular manifestation of RA presenting with skin ulcers and mononeuritis multiplex
- Diffuse pulmonary vasculitis is rare in RA, being more commonly seen in SLE
- PAH may manifest secondary to obliterative arteritis & signs of systemic vasculitis are present simultaneously

# Pulmonary-Renal Syndrome

- Association of microscopic hematuria, increasing renal insufficiency and pulmonary infiltrates raises the possibility of a pulmonary-renal syndrome
- WG, MPA, GPS, SLE
- BAL is usually hemorrhagic
- ANCAs (C-ANCA, P-ANCA), antibodies to PR-3 & MPO
- Note: RA & WG are clinically & immunologically independent diseases. Cases are described of pts with both.

# PAH

- **Idiopathic PAH (formerly PPH)**
  - Rare, incidence 1-2/million
  - thought to be related to an underlying vasculitis, and signs of a systemic vasculitis are often present simultaneously
- **Secondary PAH**
  - Usually seen in association with severe ILD
  - Associated with: Limited Systemic Sclerosis (CREST syndrome), SLE, MCTD
    - Isolated reports of assoc with dermatomyositis, APLS, RA, Sjogrens

# PAH

- Associated with an array of systemic respiratory diseases which results in an increase in pulmonary vascular pressure
- Mean resting pulmonary artery pressure  $> 25$  mmHg
- S/S: exertional dyspnea, chest pain, syncope, vertigo, palpitations, and occ cough/hoarseness
- **Dyspnea is the most frequent presenting complaint in PAH**
  - Due to impaired O<sub>2</sub> delivery during physical activity as a result of the inability to raise CO to meet increased O<sub>2</sub> requirements

# PAH

- 90% of ECG & CXR films will suggest a dx
  - ECG with right axis deviation, P waves in II & V<sub>1</sub> may peak reflecting atrial enlargement, high R waves in V<sub>1</sub> reflect RVH, inversion of T wave and ST segment depression in V<sub>1</sub>-V<sub>3</sub>
  - CXR: enlargement of pulm trunk & main branches
- 2D echo: RA and RV enlargement with paradoxical systolic motion of the interventricular septum. When TR or PR present, it is possible to estimate the pulmonary artery pressures.
- Cardiac cath: confirms pulmonary artery pressures, further evaluates valvular disease & assesses LV function. Establishes severity of PAH & allows assessment of prognosis

# WHO Functional Classification of Pulmonary Hypertension

- Class I—Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or syncope.
- Class II—Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or syncope.
- Class III—Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or syncope.
- Class IV—Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

# Diagnostic studies

- CXR
- EKG
- 2D ECHO with estimated RVSP
  - Cardiac catheterizaion
- PFTs with DLCO
  
- HRCT chest
- Lung biopsy

# Summary

- Pulm involvement is one extra-articular feature of RA with a broad ddx
- When thinking about dyspnea in a rheum pt one must think about disease-associated lung disease, drug-related lung disease and infection secondary to immunosuppression
- Overlapping clinical syndromes can include PAH and rarely vasculitides including pulm-renal syndromes
- Approach to dx does not differ greatly from dyspnea work-up: CXR, EKG, echo, PFTs. HRCT and lung bx if warranted.

# Bibliography

- Anaya, JM, et al. Pulmonary Involvement in Rheumatoid Arthritis. *Sem Arth Rheu.* 1995;(24):242-254.
- Amin NM. Cough, Chest Pain and Dyspnea in a Woman with Rheumatoid Arthritis. *Consultant.* 2007; 47 (1): 1-4.
- Daien Ci, et al. Sarcoid-like granulomatosis in patients treated with tumor necrosis factor blockers: 10 cases. *Rheumatol (Oxford).* 2009; 48:865-866.
- Hacking JC, et al. Causes and investigation of increasing dyspnoea in rheumatoid arthritis. *Ann of Rheum Dis.* 1995; 54:17-19.
- Hollingsworth HM, et al. Case 32-2001: A 77-Year-Old Man with Rheumatoid Arthritis and Acute Dyspnea and Acute Renal failure. *Case Records of Massachusetts General Hospital. N Engl J Med.* 2001; 345:1193-1200.
- Kim DS. Interstitial Lung Disease In Rheumatoid Arthritis. *Curr Opin Pulm Med.* 2006; 12(5):346-353.
- Kremers HM, Gabriel SE. Rheumatoid Arthritis and the Heart. *Curr Heart Fail Rep.* 2006;3:57-63.
- Lake, FR. Overview of lung disease associated with Rheumatoid arthritis. *UpToDate Online* 18.2
- Libby: *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 8th ed. CHAPTER 73 – Pulmonary Hypertension. Stuart Rich, Vallerie V. McLaughlin. 2007; Saunders, An Imprint of Elsevier.

# Bibliography

- McKenna F. Wegener's granulomatosis and rheumatoid arthritis overlap. *Rheum* 2002 (41)5:588.
- Niewold TB, et al. 59-Year-Old Woman With Progressive Dyspnea on Exertion. *Mayo Clin Proc.* 2004; 1567-1570.
- Nesheiwat JP, et al. An Elderly Man With Rheumatoid Arthritis and Dyspnea. *Chest.* 2009; 135:1090-1093.
- Papanikolaou, IC, et al. A 47-Year-Old Woman With Rheumatoid Arthritis and Dyspnea on Exertion. *Chest.* 2009;136: 1694-1697.
- Pappas DA, et al. A 73-Year-Old Woman with Rheumatoid Arthritis and Shortness of Breath. *Arth & Rheum.* 2008: 59(6);892-899.
- Ronnelid J, et al. Rheumatoid factor and antibodies to cyclic citrullinated peptides are associated with severe extra-articular manifestations in rheumatoid arthritis. *Ann Rheum Dis.* 2007; 66(1):59-64.
- Zeiger Roni F, McGraw-Hill's Diagnosaurus 2.0: <http://www.accessmedicine.com/diag.aspx>.