Thoracic Manifestations of Rheumatoid Arthritis: A Case-Based Approach
Cristopher A. Meyer, MD

Outline
- Pathogenesis: the lung-joint connection
- Airways
- Lung Parenchyma
- Drug Toxicity

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Rheumatoid Arthritis
- Articular Manifestations
  - Morning stiffness
  - Erosive arthritis of peripheral joints
- Serology:
  - Rheumatoid factor
  - Anti-citrullinated peptide antibodies (ACPA)
- Extra-articular Manifestations
  - Subcutaneous nodules
  - Ocular inflammation
  - Pericarditis
  - Splenomegaly (Felty syndrome)
  - Neuropsychiatric disorders

Airways and RA: ACPA Theory
- ACPA’s are highly specific for RA (95-98%) and 65-88% sensitive
- Smoking: associated with + ACPA at BAL
- Nonsmokers: 94% with (+) anti-CCP in RA have bronchiectasis (trigger?)
- Chronic P. aeruginosa infection raises heat shock protein levels (autoAb to this protein in RA, ILD)
- Airway involvement may be the earliest manifestation of RA

Small Airways Disease in RA
- 34 patients with RA < 1 yr*
  - 69% had expiratory air trapping
  - 58% bronchiectasis
  - 35% ground glass opacity
- 14 asx 1st degree relatives of RA pts**
  - 6/7 with (+) anti-CCP had air trapping at exp HRCT
  - 6/7 with (-) anti-CCP
- Key point: expiratory HRCT important in the evaluation of RA patients

** Clin Rheumatol 2009; 28: 611-613

Modified from Perry E et al Rheumatology 2014; 53. 1946-50.
RA and Airways Disease

- Bronchiectasis
  - Dilation (30-40%)
  - Bronchial wall thickening (12-92%)
- Obliterative bronchiolitis (OB)
  - Air trapping (43% of symptomatic patients)
  - Tree-in-bud (10-31%)
- Follicular bronchiolitis

Lynch DA. J Thorac Imaging 2009; 24: 299–305

FB/LIP

- Spectrum of benign lymphoproliferative disorders
- Diffuse interstitial infiltrate of small lymphocytes and plasma cells along airways and interstitium (BALT)
- Associations:
  - Sjögren’s Disease (most commonly)
  - Chronic infection
  - Collagen vascular disease (RA)
  - Familial immunodeficiency, AIDS
  - Hypersensitivity reaction

FB/LIP: HRCT Findings

- Poorly defined centrilobular or peribronchial nodules (3-12 mm)
- Ground glass opacities
- Septal thickening*
- Thickened peribronchovascular interstitium
- Perivascular cysts* usually involving <10% of lung parenchyma
- Mosaic air trapping

* Cysts non-reversible

Follicular Bronchiolitis

77-year-old female with RA for 20 years on MTX and Leflunomide
RA and ILD
- 1.3 million patients with RA in USA
  - 10% with symptomatic ILD
  - 30% additional with subclinical ILD
- Median survival after ILD dx: 2.6 yrs
- Accounts for 7% of all RA deaths
- Role of chest imaging screening is unclear
- Prognosis may relate to histopathologic phenotype


RA and ILD Risk Factors
- Advanced age
- Male sex (equal prevalence male: female)
- Severity of joint disease
- High titer rheumatoid factor
- Elevated levels of anti-citrullinated protein antibodies (ACPA's)
- Smoking

Kelly CA et al. Rheumatology 2014;53: 1676-1682

RA and ILD: Prevalence
- 103 patients (76 women and 27 men)
- Mean age 49.1 ± 14.7 yrs
- Disease duration 4.3 ± 5.7 yrs
- Mean articular disease activity score 4.4 ± 1.4
- 61% RA-ILD by HRCT and PFT's
- Clinically evident ILD in 6%

Chen J et al. Clin and Dev Immunology Volume 2013. Article ID 406927

RA and ILD
- Primary
  - Usual interstitial pneumonia (UIP)
  - Nonspecific interstitial pneumonia (NSIP)
  - Organizing pneumonia (OP)
  - Diffuse alveolar damage (DAD)
- Secondary
  - Disease Modifying Antirheumatic Drug Toxicity
  - Infection
  - Lymphoproliferative


82 y.o. male on chronic MTX and prednisone. Anti-CCP>200

RA and ILD: Prevalence
- 68 y.o. male dx'd with RA 4 yrs ago with rheumatoid nodules

RA-ILD: UIP vs. NSIP

- UIP
  - Smokers
  - Acute exacerbation
  - Worse prognosis
- NSIP
  - Nonsmokers
  - More steroid responsive

Park JH et al. Am J Respir Crit Care Med 2007; 175:705–711

Acute Exacerbation of RA-ILD

- Criteria
  - Prior diagnosis of RA-ILD
  - Unexplained worsening/development of dyspnea
  - New bilateral ground-glass abnormalities and/or consolidation superimposed on a reticular or honeycomb pattern on HRCT
  - No evidence of pulmonary infection
  - Exclusion of alternative causes of AUI such as left heart failure, pulmonary embolism
- One year incidence 2.8%
- 6/11 patients treated with MTX > 1yr
- Mortality of AE in RA-ILD was 64%

44 y.o. female dx'd with RA 2 yrs prior with increased RF and anti-CCP. OSH admit for suspected pneumonia/ARDS. BAL -

**Rheumatoid Nodules**

- Incidence: 25% of RA, lungs (1% at CXR 1%, 22% at HRCT, associated subcutaneous nodules in 80%)  
- Location: most common in subcutaneous tissues but also visceral organs (liver, eyes, heart, and lung)  
- Pathology: necrotic center marginalized by palisading histiocytes (epithelioid cells) and surrounded by plasma cells and lymphocytes  
- Findings:  
  - Solitary or multiple  
  - Few mm to few cm  
  - Wax and wane with disease activity  
  - Cavititation up to 10% (if peripheral, SRF and PTH)  
  - Calcification rarely reported in the absence of Caplan's Syndrome

77-year-old female with RA for 20 years on MTX and Leflunomide

**Differential Dx of Nodules in RA**

- Infection (immunosuppression)  
- Follicular Bronchiolitis  
- Smoking-related ILD  
- Necrobiotic nodules  
- Amyloidosis  
- Drug reaction

**Drug Toxicity in RA**

- Steroids – opportunistic infection 2º to immunosuppression  
- Methotrexate – CIP, PIE, PF, DAH  
- Gold salts – HP, DAD, PF, OP, BO  
- Penicillamine – BO, OP, DAD  
- Cyclophosphamide – OP, PF, DAD  
- Anti-TNF α group – granulomatous infection, sarcoidlike rxn, OP, PF
TNF Antagonists and Sarcoid Rxn*

- 27 cases (15 with RA)
- Women 78%, mean age 49
- ETN 52%, INF 30%, adalimumab 18%
- Mean exposure 23 months (1-60)
- Extrapulmonary findings also in 41%
- Mediastinal LAD 85%
- Nodules 67%
- 89% resolved with cessation +/- steroids (52%)

58 y.o. female with newly dx'd RA, started prednisone and MTX 2 mos prior.
6 weeks after discontinuation of MTX

57 y.o. man with 6 yrs of difficult to control RA on etanercept, hydroxychloroquine and prednisone now with fever.
Drug Toxicity: Nodulosis

- Methotrexate (8%)
- LEF (leflunomide)
- TNF alpha blockers (incidence 0.042%)*
  - Etanercept (Enbrel) – most commonly
  - Infliximab (Remicaid)
  - Adalimumab (Humira)
- *Does not mandate stopping therapy

Summary

- Airway disease is an early manifestation of RA. Expiratory HRCT essential.
- Risk factors for RA-ILD: male, smoker and (+) ACPA
- UIP pattern in 2/3 correlated with 2X increased mortality
- Drug toxicity include fibrosis, OP and nodulosis/sarcoid reaction

Toussirot E et al. J Rheumatol 2009; 36: 2421-2427