Immunologic Fingerprint in Rheumatoid Arthritis: the Lungs, Culprit or Victim?

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Disclosures

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Objectives

- Summarize recent theory that autoimmunity rheumatoid arthritis (RA) is initiated in the lung
- Illustrate early and classic chest CT manifestations of RA
- Emphasize importance of expiratory imaging in the detection of small airways disease
- Highlight importance of serology and lung histopathology with respect to prognosis in RA
- Outline treatment goals and elucidate treatment-related complications particularly lung toxicity
Introduction

- RA affects 0.5-1% of adults worldwide
- 10% will have clinically evident interstitial lung disease (RA-ILD)
- Autoimmunity may develop in the lung as a result of environmental exposures such as cigarette smoke
- Serology and histopathology impact prognosis of RA-ILD
- Early treatment may prevent advanced destructive disease and improve likelihood of remission
ACR/EULAR Criteria for RA

- Criteria score includes joint involvement, duration of symptoms, serology, and acute phase reactants

Serology is a **KEY** component of the new criteria score:

- Rheumatoid factor (RF):
  - Sensitivity 69%, Specificity 85%
- Anti-cyclic citrullinated peptides (ACPA):
  - Sensitivity 67%, Specificity 95-98%

Increased frequency of early lung inflammation

- Seropositive RA occurs in 70-80% of patients
- Seronegative RA may be a different disease
BALT & ACPA: The Evidence

- Bronchus-associated lymphoid tissue (BALT) responds to local insult by generating IgA antibodies including RF and ACPAs
- Pathologic appearance is similar to RA joint nodules
- Smoking = ↑ ACPAs in BAL fluid
- 94% of nonsmokers with RA and bronchiectasis have ACPAs³

ACPA+ disease = increased frequency of lung inflammation

BALT with lymphoid follicle ( ), germinal center ( ) and airway ( * ).

Courtesy of Scott Aesif, MD, (Dept. of Pathology, Madison, WI)
Genetic predisposition

Environmental exposure

HLA-DRB1 SE

Trauma

Inflammation

Initial Insult

Citrullinated peptides

Develop

ACPAs

Secondary Insult

Citrullinated synovial peptides

B cells activated ➔ ↑ACPAs and IgM isotypes; smokers have increased BALT ➔ production of RF and ACPA

RA Airway Manifestations

- Bronchial wall thickening 12-92%
- Air trapping in 43% of symptomatic patients
- Tree-in-bud opacities 10-31%
- Bronchiectasis 30-40%

Expiratory CT helpful to detect mild air trapping from early small airways involvement\(^5\)

HRCT shows bronchiectasis (\(\rightarrow\)) and mosaic attenuation (\(\leftarrow\)) reflecting air trapping.

Courtesy of Donald Yandow, MD. (Madison, WI.)
Small Airways Disease (SAD)

Airway involvement may be the **earliest** lung manifestation of RA

- In 34 patients diagnosed with RA < 1 year:
  - 69% expiratory air trapping
  - 58% bronchiectasis
  - 35% ground-glass opacities

- In 14 asymptomatic 1<sup>o</sup> relatives of RA patients air trapping was present in:
  - 6/7 with (+) ACPA
  - 0/7 with (-) ACPA

HRCT images show areas of decreased attenuation 反映 air trapping.
Rheumatoid Nodules and SAD

53 F with scattered rheumatoid nodules (→) and mosaic attenuation.

Expiratory images confirm air trapping (←).

Courtesy of Santiago Rossi, MD. (Buenos Aires, Argentina)
Follicular Bronchiolitis

- Benign lymphoproliferative disorder
- Diffuse infiltrate of small lymphocytes and plasma cells along airways and interstitium
- HRCT Findings:
  - Poorly-defined centrilobular or peribronchial nodules (3-12 mm)
  - Ground-glass opacities
  - Thickening of septa and peribronchovascular interstitium
  - Perivascular cysts (<10% of lung)
  - Air trapping

Follicular bronchiolitis (FB) is airway-centric with focal peribronchial lymphoid hyperplasia while lymphoid interstitial pneumonia (LIP) is more diffuse interstitial involvement.

43 F with peribronchovascular nodules (→) and thickening of bronchovascular bundles (→).
77 F with RA for 20 years treated with methotrexate and leflunomide. Centrilobular ground-glass nodules (→) were FB at pathology in biopsy specimen performed for other reasons.
59 M smoker with RA for 10 years treated with adalimumab with lower lobe predominant variable sized ground-glass nodules (→), scattered thin walled cysts (←), and thickening of the bronchovascular bundles (→).
82 M with elevated ACPA(+) RA on MTX and prednisone with perivascular cysts (→) and poorly-defined ground-glass nodules (←).
RA-ILD

- 1.3 million patients with RA in USA
  - Symptomatic ILD in 10%
  - Subclinical ILD in 30-61%\(^8\)
- Median survival after ILD diagnosis: 2.6 years
- RA-ILD accounts for 7% of all RA deaths
- Over 80% of patients with RA related pulmonary disease die from pulmonary complications\(^9\)
- Early detection may not impact disease course or alter treatment decisions

71 M with RA for 8 years with elevated RF and ACPAs > 200 with UIP.
ILD by CTD Subtype

- Primary\textsuperscript{10}
  - Usual interstitial pneumonia (UIP)
  - Nonspecific interstitial pneumonia (NSIP)
  - Organizing pneumonia (OP)
  - Diffuse alveolar damage (DAD)

- Secondary
  - Disease modifying anti-rheumatic drug toxicity
  - Infection
  - Lymphoproliferative processes

Prevalence of NSIP compared with UIP may be artificially elevated as biopsies are typically not obtained when classic UIP pattern is present.

RA-ILD
Risk Factors

- Advanced age
- Smoking
- Male
- Severity of joint disease
- High titer RF
- Elevated levels of ACPAs\textsuperscript{12}

66 M with UIP characterized by subpleural and basal predominant reticulation and honeycombing (→).
Evolution of NSIP Pattern

A NSIP pattern of lung disease is associated with improved survival as compared with a UIP pattern.¹³

59 M smoker with RA for 10 years treated with adalimumab. Serial HRCT demonstrates evolution of NSIP with increasing ground-glass opacities, reticulation (→), and mild traction bronchiectasis (←).
RA-ILD: UIP vs. NSIP

- **UIP**
  - Smokers
  - Acute exacerbation
  - Worse prognosis

- **NSIP**
  - Nonsmokers
  - More steroid responsive

**Histopathologic type =**

**Prognosis**

**Mortality:**
IPF > RA-ILD UIP > non-UlP ILD

Interstitial pneumonia with autoimmune features (IPAF): combination of features from 2 of 3 domains\textsuperscript{15}
- **Clinical** domain – extrathoracic features
- **Serological** domain – specific autoantibodies
- **Morphological** domain – specific chest imaging, histopathological, or pulmonary features

IPAF criteria may include patients with RA where lung manifestations **predate** other manifestations of RA or CTD-ILD

Clinical & serological domains may have greater prognostic significance in possible UIP on HRCT when surgical lung biopsy is impractical

57 F with incompletely defined autoimmunity presenting with dyspnea. CT shows patchy peripheral and peribronchial consolidation (→) and ground-glass opacity typical of organizing pneumonia.

Mortality: IPF > IPAF > CTD-ILD
RA-ILD: Acute Exacerbation

Diagnostic criteria:

1. Prior diagnosis of RA-ILD
2. Unexplained development or worsening of dyspnea
3. New lung opacities superimposed on lung fibrosis
4. No evidence of pulmonary infection
5. Exclusion of alternative causes of acute respiratory illness such as heart failure, drug toxicity, or pulmonary embolism

44 F with RA for 2 years with increased RF titer and ACPA levels presents with respiratory distress. AP radiograph shows diffuse lung opacity.
RA-ILD: Acute Exacerbation

- 1 year incidence in RA-ILD 2.8%
- 6 of 11 patients were treated with MTX > 1 year
- Mortality of AE in RA-ILD is high (64%)\(^{16}\)
- DDx:
  - Treatment-related drug toxicity
  - Infection

44 F with RA for 2 years with increased RF titer and ACPA levels presents with respiratory distress. BAL was negative. CT shows diffuse ground-glass opacities (→) and a small right pneumothorax (→).
Management Goals

Treatment:
- Corticosteroids
- Immunomodulating, steroid-sparing agents, or both
- Smoking cessation
- Pulmonary rehabilitation
- Supplemental oxygen
- Pneumococcal and influenza vaccines

Evaluate for comorbidities:
GERD and pulmonary hypertension as CTD-ILD has better prognosis

Windows of Opportunity —
- Treating early when burden of “diseased cells” is lower for greater response
  Ideally within 6 months

Treat to Target = remission

78 M with RA and enlarged main pulmonary artery (★), indicating pulmonary hypertension.
RA Therapy Complications

Immunosuppression
- Corticosteroids - opportunistic infection
- Biologic DMARDs - granulomatous infection

Drug Toxicity$^{17}$
- NSAIDS - eosinophilic pneumonia
- Nonbiologic disease-modifying antirheumatic drugs (DMARDs)
  - Methotrexate: chronic interstitial pneumonia (CIP), pulmonary opacities with emphysema, pulmonary fibrosis, diffuse alveolar hemorrhage
  - Cyclophosphamide: organizing pneumonia, pulmonary fibrosis, diffuse alveolar damage
- Biologic DMARDs
  - Anti-TNF-α group – granulomatous opportunistic infection, sarcoid-like reaction, organizing pneumonia, pulmonary fibrosis, lymphoma
Drug-Induced Immunosuppression

68 F with RA on infliximab with pulmonary hypertension, and asthma presenting with nocardiosis and aspergillosis. CT images show multifocal peribronchial consolidation and scattered nodules (→).
NSAID-Induced Eosinophilic Pneumonia

47 M with RA on naproxen with progressive dyspnea on exertion. CT images show patchy upper lung predominant peripheral consolidation (→) and ground-glass opacities. Mild reticulation (→) in the bases suggests early lung fibrosis.
58 F with newly diagnosed RA on prednisone and MTX for 2 months presents with dyspnea. HRCT shows peripheral reticulation (→), septal thickening (←), and diffuse ground-glass opacities (→).

HRCT 6 weeks later shows clearing of ground-glass opacity following cessation of MTX.
In a study with 27 patients (15 with RA) treated with TNF-α antagonists with a mean exposure of 23 months:

- Extrapulmonary findings - 41%
- Mediastinal lymphadenopathy - 85%
- Nodules - 67%
- 89% of cases resolved with cessation +/- steroids (52%)
- TNF-α antagonists used including etanercept 52%, infliximab 30%, adalimumab 18%

57 M with 6 years of difficult to control RA on etanercept, hydroxychloroquine, and prednisone presenting with fever and upper zone predominant nodules.
Treatment Related Effects:
Sarcoid-like reaction (etanercept nodulosis)

CT images show small nodules in the upper lobes with a perilymphatic distribution simulating sarcoidosis. Infectious work-up was negative.
Lungs may be the site of inciting immunologic insult in rheumatoid arthritis.

Small airways disease may be the earliest lung manifestation of RA and is best detected by expiratory CT.

RA-ILD UIP has a high mortality.

DMARDs may result in significant lung toxicity.

Goals:
- Current: early diagnosis and treatment to achieve remission
- Future: identify and treat lung disease prior to joint involvement?
## Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACPA/Anti-CCP</td>
<td>anti-citrullinated protein antibodies</td>
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<td>BAL</td>
<td>bronchoalveolar lavage</td>
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<td>BALT</td>
<td>Bronchus-associated lymphoid tissue</td>
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<tr>
<td>CB</td>
<td>constrictive bronchiolitis</td>
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<tr>
<td>CIP</td>
<td>chronic interstitial pneumonia</td>
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<tr>
<td>DAD</td>
<td>diffuse alveolar damage</td>
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<tr>
<td>DAH</td>
<td>diffuse alveolar hemorrhage</td>
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<tr>
<td>DMARDS</td>
<td>disease-modifying antirheumatic drugs</td>
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<td>FB</td>
<td>follicular bronchiolitis</td>
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<td>hypersensitivity pneumonitis</td>
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<td>HRCT</td>
<td>high resolution computed tomography</td>
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<td>ILD</td>
<td>interstitial lung disease</td>
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<td>IPAF</td>
<td>interstitial pneumonia with autoimmune features</td>
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<td>LIP</td>
<td>lymphoid interstitial pneumonia</td>
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<td>MTX</td>
<td>methotrexate</td>
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<td>OP</td>
<td>organizing pneumonia</td>
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<td>pulmonary fibrosis</td>
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<td>pulmonary interstitial emphysema</td>
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<td>RA</td>
<td>rheumatoid arthritis</td>
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<td>RF</td>
<td>rheumatoid factor</td>
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References