Diagnosis of Connective Tissue Disease – Interstitial Lung Disease in 2016

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Speaker Disclosure

• In accordance with the policy of the Thoracic Society of Australia and New Zealand the following presenter has indicated that they have a relationship which in the context of their presentation, could be perceived as a real or apparent conflict of interest but do not consider that it will influence their presentation. The nature of the conflict is listed:

• Personal financial relationships with commercial interests relevant to this presentation during the past 12 months:
  • Consultant/Advisory Board: Boehringer Ingelheim, AstraZeneca, Roche
  • Travel/Speaker fees: Boehringer Ingelheim
  • Funding for the B-PHIT trial received from Actelion Pharmaceuticals (2006-2010)

• Relevant institutional financial interests
  • Research funding: Boehringer Ingelheim, Roche, Gilead, Bayer, Actelion, InterMune Pharmaceuticals)
Outline of Today’s Talk

• Background:
  – Common ILD subtypes in CTD
  – Prognosis of CTD-ILD
  – Approach to CTD-ILD Diagnosis

• 2015-6 Landmark Papers
  – Clinical features
  – Autoimmune Serology
  – Idiopathic Pneumonia with Autoimmune Features
  – Prognosis

• Questions
BACKGROUND
Interstitial Lung Disease

ILD of Known Association
- CTD-ILD
  - Drugs
  - Occupational exposure

Granulomatous Lung Disease
- Sarcoid Hypersensitivity Pneumonitis

Idiopathic Interstitial Pneumonias
- Major IIP
  - IPF (UIP), NSIP, OP, RBILD, DIP, AIP
- Rare IIP
  - LIP
  - IPPF
- Unclassifiable

MiscellaneousILD
- LAM
- Histiocytosis X
Specific CTD associated with ILD

- Scleroderma
- Rheumatoid arthritis
- Dermatopolymyositis
- Systemic lupus erythematosus
- Sjogren’s syndrome
- Mixed connective tissue disease
- Vasculitides

- Undifferentiated ("Interstitial pneumonia with autoimmune features", IPAF)
ILD Patterns in CTD

- **NSIP** is the most common pattern in CTD
- Also see **UIP, OP, LIP, AIP**
- Often see a combination of ILD patterns, and additional airway and pleural disease
Effect of CTD on Prognosis

- CTD is associated with better outcomes compared to idiopathic NSIP or IPF

Flaherty et al 2003

Park JH et al 2007
Effect of ILD Pattern on Prognosis

Idiopathic Interstitial Pneumonia

Scleroderma ILD

Flaherty et al, 2002

Bouros et al, 2002

Not significant
Approach to CTD-ILD Diagnosis

• Known CTD
  ➢ CTD diagnosis
  ➢ ILD pattern

• No Known CTD
  – *Detailed assessment to uncover CTD*
  – History and Examination
    • Rashes,
    • alopecia,
    • arthralgia/arthritis,
    • muscle pain/weakness,
    • GORD/dysphagia,
    • Sicca symptoms,
    • Raynaud’s
  – Serology
  – Nail fold capillaroscopy
Auto-antibodies

- RF
- Anti-CCP
- ANA
- ENA
- dsDNA
- CK
- C3, C4

- Ro-52
- Anti-U1 RNP
- PM-Scl
- Ku

- Jo-1
- OJ
- EJ
- PL-12
- PL-7
- Mi-2
- SRP

Myositis associated antibodies

Myositis specific antibodies
What we don’t know

• Which tests to perform?

• How often to repeat testing?

• What the implications of positive tests are for the IPAF patient?
  – Treatment? Prognosis?
LANDMARK PAPERS 2015-6

And an interesting review article.
Clinical Characteristics of Connective Tissue Disease-Associated Interstitial Lung Disease in 1,044 Chinese Patients

Yang Hu, PhD; Liu-Sheng Wang, MD; Ya-Ru Wei, MD; Shan-Shan Du, MS; Yu-Kui Du, MS; Xian He, MS; Nan Li, PhD; Ying Zhou, PhD; Qiu-Hong Li, MS; Yi-Liang Su, MS; Fen Zhang, MS; Li Shen, MS; Dong Weng, PhD; Kevin K. Brown, MD, PhD; and Hui-Ping Li, MD, PhD

Clinical Characteristics of CTD-ILD

• **Aim:** to determine the prevalence and the clinical features of CTD-ILD in China

• **Design:** Retrospective study of all ILD patients at Shanghai Pulm Hospital ‘99-2013
  – All admitted to hospital
  – Follow up 3-6mthly to Dec 2013 with lung function, examination and serology testing

*Chest. 2016 Jan;149(1):201-8.*
Clinical Characteristics of CTD-ILD

- 2678 ILD patients
  - 67% CTD-ILD
  - 11.2% IPF
Misdiagnosis Common

- 32% of 1044 with CTD-ILD were not diagnosed accurately at the initial visit.
  - Higher for those with pulmonary symptoms as the first presentation
    - 56% with CCTD-ILD and 65% with UCTD-ILD

- Mean time to final diagnosis 18.3 months

<table>
<thead>
<tr>
<th>Groups</th>
<th>Initial Clinical Manifestation</th>
<th>Received Diagnosis at Initial Visit, No. (%)</th>
<th>Received Diagnosis at Follow-up Examinations, No. (%)</th>
<th>Mean Time to Final Diagnosis, mo ±</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCTD-ILD</td>
<td>PSIM (n = 41)</td>
<td>18 (44)</td>
<td>23 (56)</td>
<td>17.5 ± 5.9</td>
</tr>
<tr>
<td></td>
<td>EPSIM (n = 247)</td>
<td>218 (88)</td>
<td>29 (12)</td>
<td>12.7 ± 4.3</td>
</tr>
<tr>
<td>UCTD-ILD</td>
<td>PSIM (n = 333)</td>
<td>117 (35)</td>
<td>216 (65)</td>
<td>19.9 ± 7.0</td>
</tr>
<tr>
<td></td>
<td>EPSIM (n = 423)</td>
<td>359 (85)</td>
<td>64 (15)</td>
<td>15.4 ± 4.7</td>
</tr>
<tr>
<td>Total</td>
<td>1,044</td>
<td>712 (68)</td>
<td>332 (32)</td>
<td>18.3 ± 6.8</td>
</tr>
</tbody>
</table>
Seroconversion Common

• For patients with pulmonary signs as the initial manifestation:
  – 51.2% of CCTD and 46.8% of UCTD seroconverted during follow up

• Most common antibodies seroconverting:
  – RF; SSA/B; Jo-1; Scl-70

<table>
<thead>
<tr>
<th>Groups</th>
<th>Initial Clinical Manifestation</th>
<th>Positive at Initial Visit, No. (%)</th>
<th>Positive at Follow-up Examinations, No. (%)</th>
<th>Mean Time of Positive Conversion at Follow-up Examinations, Mean ± SD (range), mo</th>
<th>Persistent Negative, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCTD-ILD</td>
<td>PSIM (n = 41)</td>
<td>8 (19.5)</td>
<td>21 (51.2)</td>
<td>11.8 ± 6.3 (6-24)</td>
<td>12 (29.3)</td>
</tr>
<tr>
<td></td>
<td>EPSIM (n = 247)</td>
<td>174 (70.4)</td>
<td>24 (9.7)</td>
<td>10.6 ± 5.2 (3-18)</td>
<td>49 (19.8)</td>
</tr>
<tr>
<td>UCTD-ILD</td>
<td>PSIM (n = 333)</td>
<td>93 (27.9)</td>
<td>162 (48.6)</td>
<td>16.0 ± 6.0 (5-24)</td>
<td>78 (23.4)</td>
</tr>
<tr>
<td></td>
<td>EPSIM (n = 423)</td>
<td>312 (73.8)</td>
<td>55 (13.0)</td>
<td>16.0 ± 5.2 (6-24)</td>
<td>56 (13.2)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,044</td>
<td>587 (56.2)</td>
<td>15.2 ± 6.0 (3-24)</td>
<td>195 (18.7)</td>
</tr>
</tbody>
</table>
Conclusions

- CTD-ILD often received an inaccurate diagnosis at the initial hospital admission, possibly because of the absence of obvious extrapulmonary symptoms and negative test results for serologic autoantibodies.

- ILD should be examined for extrapulmonary signs and symptoms and tested for autoantibodies during follow-up examinations.
Detection of Rheumatoid Arthritis–Interstitial Lung Disease Is Enhanced by Serum Biomarkers

Tracy J. Doyle¹, Avignat S. Patel¹, Hiroto Hatabu²,³, Mizuki Nishino²,³, Guodong Wu⁴, Juan C. Osorio¹, Maria F. Golzarri¹, Andres Trasloscheros¹, Sarah G. Chu¹, Michelle L. Frits⁵, Christine K. Iannaccone⁵, Diane Koontz⁶, Carl Fuhrman⁷, Michael E. Weinblatt⁵, Souheil Y. El-Chemaly¹, George R. Washko¹, Gary M. Hunninghake¹,², Augustine M. K. Choi⁹, Paul F. Dellaripa⁵, Chester V. Oddis⁶, Nancy A. Shadick⁵, Dana P. Ascherman¹⁰, and Ivan O. Rosas¹,⁴

¹Pulmonary and Critical Care Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts; ²Center for Pulmonary Functional Imaging, ³Department of Radiology, ⁴Division of Rheumatology, Immunology and Allergy, and ⁵Channing Laboratory, Brigham and Women’s Hospital, Boston, Massachusetts; ⁶Lovelace Respiratory Research Institute, Albuquerque, New Mexico; ⁷Division of Rheumatology and Clinical Immunology and ⁸Department of Radiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; ⁹Department of Medicine, New York-Presbyterian Hospital, Weill Cornell Medical College, New York, New York; and ¹⁰Division of Rheumatology, University of Miami Miller School of Medicine, Miami, Florida
Predictors of RA-ILD

- **Aim:** to identify risk factors, autoantibodies and biomarkers predicting the presence of RA-ILD.

- **Design:** Subjects enrolled in 2 large RA studies (BRASS; ACR) were assessed for ILD.
Predictors of RA-ILD

189 RA patients

No ILD 51 (26.9%)

Indeterminate ILD 53 (28%)

RA-ILD 83 (43.9%)

Subclinical ILD 47 (24.8%)

Clinical ILD 36 (19%)
Predictors of RA-ILD

– Clinical:
  • Age*, gender, ever-smoking

– Autoantibodies
  • RF* – higher in subclinical disease than clinically evident disease
  • Anti-CCP increased with severity of RA-ILD

– Biomarkers:
  • MMP7*, SP-D increased with severity of RA-ILD
  • PARC highest in subclinical disease
Predictors of RA-ILD

- Combination of clinical risk factors, autoantibodies and biomarkers increased the AUC for RA-ILD to 0.97

Spectrum of RA-ILD

Clinically evident RA-ILD

Subclinical RA-ILD
Conclusions

• A combination of clinical risk factors (older age, male sex, ever-smoking) and autoantibodies (RF, anti-CCP) is strongly associated with the presence of clinical and subclinical RA-ILD.

• An investigational biomarker signature composed of MMP7, PARC, and SP-D significantly enhances the ability to identify RA-ILD.
An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features

Aryeh Fischer¹,¹⁷,¹⁸, Katerina M. Antoniou², Kevin K. Brown³, Jacques Cadranel⁴, Tamera J. Corte⁵,¹⁸, Roland M. du Bois⁶, Joyce S. Lee⁷,¹⁸, Kevin O. Leslie⁸, David A. Lynch⁹, Eric L. Matteson¹⁰, Marta Mosca¹¹, Imre Noth¹², Luca Richeldi¹³, Mary E. Strek¹²,¹⁸, Jeffrey J. Swigris³,¹⁸, Athol U. Wells¹⁴, Sterling G. West¹⁵, Harold R. Collard⁷,¹⁸,¹⁹ and Vincent Cottin¹⁶,¹⁸,¹⁹, on behalf of the “ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD”
Interstitial Pneumonia with Autoimmune Features (IPAF)

1. Nomenclature (Sept 9, 2013): Interstitial Pneumonia with Autoimmune Features (IPAF)
2. Combination of clinical manifestations, serology, and morphological characteristics of the interstitial pneumonia → research statement

Courtesy of Prof V Cottin
IPAF Classification

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) and,

2. Exclusion of alternative aetiologies and,

3. Incomplete features of a defined CTD and,

4. At least one variable from two of these three domains:
   a. Clinical domain
   b. Serological domain
   c. Morphological domain
Clinical domain

- Raynaud’s phenomenon
- Palmar telangectasia
- Distal digital fissuring (i.e. ‘mechanic hands’)
- Distal digital tip ulceration
- Inflammatory arthritis or polyarticular morning joint stiffness ≥ 60 minutes
- Unexplained digital edema
- Unexplained fixed rash on the digital extensor surfaces.
Serologic domain

- ANA $\geq 1:320$ titer, diffuse, speckled, homogeneous patterns or
- ANA nucleolar pattern (any titer) or
- ANA centromere pattern (any titer)
- Anti-CCP $>2\times$ULN
- Anti-Ro (SS-A)
- Anti-topoisomerase (Scl-70)
- Anti-tRNA synthetase (Jo-1, PL-7, PL-12, etc.)
- Anti-PM-Scl
- Anti-CADM (MDA-5)
- Anti-La (SS-B)
- RF $\geq 2\times$ULN
- Anti-dsDNA

- Anti-RNP
- Anti-Smith
Morphologic Domain

Radiology features on HRCT
- Suggested NSIP pattern
- Suggested OP pattern
- Suggested mixed NSIP/OP pattern
- Suggested LIP pattern

Histopathology features on surgical lung biopsy
- NSIP, fOP, LIP pattern
- Interstitial lymphoid aggregates with germinal centers
- Diffuse lymphoplasmacytic infiltration (w/ or without lymphoid follicles)
- Pleuritis (acute or chronic)
- Follicular bronchiolitis

“Multi-compartment” involvement: one other compartment in addition to IP
- Unexplained pleural disease or pericardial effusion or thickening
- Unexplained small airways disease by HRCT or unexplained airflow obstruction by lung function
- Unexplained pulmonary vasculopathy (eg by disproportionately low Kco)
IPAF: What does this mean?

• Consensus Term:
  – Undifferentiated CTD associated ILD (UCTD-ILD)
  – Lung-dominant CTD
  – Autoimmune-featured ILD

• Allows further characterisation of this group:
  – Prevalence
  – Prognosis
  – Treatment
Survival in interstitial pneumonia with features of autoimmune disease: A comparison of proposed criteria

Deborah Assayag, Eunice J. Kim, Brett M. Elicker, Kirk D. Jones, Jeffrey A. Golden, Talmadge E. King Jr., Laura L. Koth, Anthony K. Shum, Paul J. Wolters, Harold R. Collard, Joyce S. Lee, *
Proposed IPAF Criteria

• 119 ILD patients with chronic fibrosing IP

• 4 different criteria for ‘IPAF’ were applied

• Considerable overlap demonstrated
Survival

- IPAF patients had improved survival compared to true IP (p=0.03-0.1).
- After adjusting for disease severity only the Corte criteria was an independent predictor of survival (p=0.04).
Conclusions

• IPAF may be associated with improved survival depending on which criteria is used to define the population.

• IPAF definition needs standardisation and evaluation.
HOW CAN WE APPLY THESE FINDINGS?
Review article

The use of auto-antibody testing in the evaluation of interstitial lung disease (ILD) — A practical approach for the pulmonologist

Thomas Bahmer a,*, Micaela Romagnoli b, Francesco Girelli c, Martin Claussen a, Klaus F. Rabe a

a LungenClinic Grosshansdorf, Airway Research Center North (ARCN), German Center for Lung Research (DZL), Woehrendamm 80, 22927 Grosshansdorf, Germany
b Pulmonology Unit, S’Orsola-Malpighi Hospital, University of Bologna, via Albertoni 15, 40138 Bologna, Italy
c Rheumatology Unit, internal Medicine Department, G8 Morgagni – L Pierantoni Hospital, Via Carlo Forlanini 34, 47121 Forlì, Italy
A practical approach…

• The diagnostic value of autoantibody testing in excluding CTD-ILD is unclear

• Recommendations regarding single autoantibody tests or the necessity to repeat autoantibody testing are lacking.
A practical approach…

• Step wise rational approach to testing
• Interdisciplinary consensus based on:

  1. Evidence for individual antibody testing;
  2. Expert opinion and
  3. Economic considerations
Algorithm

Basic laboratory testing and Follow-Up

- **ANA (IIF)**
- **AND**
  - **Jo-1**
    - Myositis / ASS
  - **SSA (Ro52 Ro60)**
  - **SSB (La)**
    - Sjögren Syndrome
  - **AND**
  - **RF**
  - **CCP**
    - RA
  - **AND**
  - **ANCA (IIF)**
    - MPA

Positive

- Signs and symptoms suspicious of:
  - MCTD
  - SLE
  - Systemic Sclerosis
  - CREST

Advanced laboratory testing
- **U, RNP**
- **Sm ds-DNA**
- **Topo-I, Th/To, CENP-B RNA Polymerase III**

Negative

- Signs and symptoms suspicious of:
  - ASS
  - Myositis
  - Overlap Syndrome

Positive

- MPO-ANCA (EIA)

Rheumatologist and Multidisciplinary Approach

Positive Results

Negative Results

Follow-Up

Positive Results

Negative Results
Conclusions

• Local adaption of algorithm

• Rational and stepwise approach of serological testing for ILD

• Save unnecessary expenses associated with general laboratory screening.

• A consensus on the strategy for laboratory testing in ILD is needed
Problem with this approach

• Will miss IPAF patients
  – Significant number of patients will have positive testing without extrapulmonary symptoms/signs
Take Home Messages

• The presence of underlying CTD *DOES* matter

• The ILD subtype does *NOT* really matter in CTD

• Careful diagnostic assessment for CTD is important in the ILD patient
  – Screening; Diagnosis; Prognosis; Treatment

• New terminology - Idiopathic Pneumonia with Autoimmune Features
  – Further Evaluation; Prognostic and Treatment implications
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  – Dr Annabelle Mahar; (Pathology)
  – Dr Lauren Troy (RPAH, Sydney)
  – Prof Jane Bleasal (University of Sydney, RPAH)

• Dr Aryeh Fischer (National Jewish Hospital, USA)
• Prof Vincent Cottin (University Hospital of Lyon, France)
Questions...