Polyautoimmunity
Diagnosis and Significance

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Polyautoimmunity:

- Autoimmune diseases (ADs) co-occurring within patients.
- **Multiple Autoimmune Syndrome**: 3 or more ADs in the same patient.
- Other terms: “associated”, “overlap syndrome”, “coexistent” “secondary”
Multiple Autoimmune Syndromes

Les syndromes auto-immuns multiples (S.A.M.)


Three or more well defined autoimmune diseases in a single patient

Polyautoimmunity

- Polyautoimmunity in RA, SS, SLE, and other autoimmune diseases.
- Factors influencing polyautoimmunity
- Does polyautoimmunity influence the severity of autoimmune diseases?
Polyautoimmunity in Rheumatoid Arthritis

- 130/955 (13.6%) patients disclosed polyautoimmunity.
- 161 additional ADs were observed.
  - AITD 76 (8%)
  - SS 50 (5.2%)
  - SLE 24 (2.5%)
  - MAS 23 (2.4%)
- Factors influencing polyautoimmunity in RA:
  - Familial autoimmunity, Familial RA, and toxics.
- Multiple autoimmune syndrome was associated with extra-articular manifestations.

Anaya JM, et al. EULAR 2015 THU0152
Familial Autoimmunity and Polyautoimmunity in RA

When familial autoimmunity was present, the risk of developing polyautoimmunity was similar in men and women, whereas the risk of polyautoimmunity without FAI was higher in women than in men.

Anaya JM, et al. EULAR 2015 THU0152
Familial RA and Polyautoimmunity

Anaya JM, *et al.* EULAR 2015 THU0152
Toxics and Polyautoimmunity in RA

Anaya JM, et al. EULAR 2015 THU0152
Multiple Autoimmune Syndrome and extra-articular manifestations in RA

Anaya JM, et al. EULAR 2015 THU0152
Rhupus (SLE&RA)

Characteristics of patients with Rhupus
(as compared with SLE patients)

- Older
  \((46.42 \pm 13.47 \text{ vs. } 36.37 \pm 13.47 \text{ yrs, } p <0.001)\)
- Later age at onset of the disease
  \((35.9 \pm 15.25 \text{ vs. } 28.84 \pm 12.58 \text{ yrs, } p=0.017)\).
- Similar duration of the disease
  \((9 \pm 7.5 \text{ vs. } 7.5 \pm 7.3 \text{ years, } p=0.3)\).
- The mean age at onset of RA was
  \(30 \pm 11.63 \text{ yrs.}\)
- RA preceded SLE in 15 patients (62.5%).
- The PPV and NPV of anti-CCP3 for rhupus were 0.62 and 0.91 respectively.

Polyautoimmunity in Systemic Lupus Erythematosus

Factors Influencing Polyautoimmunity in Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Variable</th>
<th>AOR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>2.30</td>
<td>1.03</td>
<td>5.15</td>
</tr>
<tr>
<td>Articular involvement</td>
<td>2.02</td>
<td>1.26</td>
<td>3.23</td>
</tr>
<tr>
<td>Familial autoimmunity</td>
<td>1.61</td>
<td>1.14</td>
<td>2.28</td>
</tr>
<tr>
<td>Anti-Ro Ab</td>
<td>1.54</td>
<td>1.10</td>
<td>2.16</td>
</tr>
<tr>
<td>Origin (Colombia vs Spain)</td>
<td>1.78</td>
<td>1.40</td>
<td>2.27</td>
</tr>
</tbody>
</table>

Does ancestry influence polyautoimmunity?
Influence of Ancestry on Polyautoimmunity

- **Population:** 508 individuals: 240 single autoimmune disease, 51 with polyautoimmunity, 36 with MAS, and 181 matched-controls.
- Marshfield Screening Set 16. 353 STRs, **32 AIMs**.
- The individual Admixture map was built using **STRUCTURE 2.3.4**
- The number of cluster was set in 3, the number of burn-in simulations was set in 5000 and 100000 simulations for inference.
- A MANOVA model on arl transformed ancestral profiles was adjusted to evaluate differences in ancestral profiles among different cases (AD, POLY and MAS) and controls.

Molano-González N et al. Submitted
Ameridian Ancestry Influences Polyautoimmunity

Reference populations and Colombian population.

Colombian population by autoimmune disease status.

Molano-González N et al. Submitted
Ameridian Ancestry Influences Polyautoimmunity

Molano-González N et al. Submitted
Autoimmune Thyroid Disease in Systemic Lupus Erythematosus

Autoimmune Thyroid Disease in Systemic Lupus Erythematosus

Sjögren's syndrome and smoking are predictive factors associated with the development of AITD in SLE

# Polyautoimmunity in Sjögren's Syndrome

<table>
<thead>
<tr>
<th>Autoimmune Diseases</th>
<th>Prevalence N = 410 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS alone</td>
<td>275 (67)</td>
</tr>
<tr>
<td>SS + AD (Polyautoimmunity)</td>
<td>135 (33)</td>
</tr>
<tr>
<td>SS + 1 AD</td>
<td>101 (24.6)</td>
</tr>
<tr>
<td>SS + 2 or more ADs (MAS)</td>
<td>35 (8.5)</td>
</tr>
</tbody>
</table>

## Polyautoimmunity in Sjögren's Syndrome

N=410

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SS alone N=276</th>
<th>SS – PA N=134</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>4 (6)</td>
<td>7.86 (7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>46.7 ± 14.8</td>
<td>47.9 ± 14.2</td>
<td>0.95</td>
</tr>
<tr>
<td>Age at onset</td>
<td>45.4 ± 13.8</td>
<td>43.3 ± 13.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Polyautoimmunity in Sjögren's Syndrome

Polyautoimmunity in Sjögren's Syndrome MAS cases

Prevalence

SS-AITD-SLE: 8
SS-AITD-RA: 7
SS-SLE-APS: 6
SS-SLE-RA: 6

## Polyautoimmunity in Sjögren's Syndrome

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<tr>
<th>Characteristic</th>
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</thead>
<tbody>
<tr>
<td>Positive smoking status</td>
<td>27.6</td>
<td>51.5</td>
<td>2.86</td>
<td>1.18-6.94</td>
<td>0.02</td>
</tr>
<tr>
<td>Spontaneous abortions</td>
<td>2.1</td>
<td>17.5</td>
<td>10.87</td>
<td>1.47-80.08</td>
<td>0.02</td>
</tr>
<tr>
<td>ANAs (+)</td>
<td>83</td>
<td>93.5</td>
<td>8.55</td>
<td>1-73.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Polyautoimmunity in SSc, PBC, Vitiligo, AITD and MS

Systemic Sclerosis. 38%

Primary Biliary Cirrhosis. 32%

Vitiligo. 27%

Myastenia Gravis. 13%

Autoimmune Thyroid Diseases. 14%

Multiple Sclerosis. 8%
Clustering of autoimmune diseases is not random

Polyautoimmunity

- Polyautoimmunity in SS, SLE, and other autoimmune diseases
- Multiple Autoimmune Syndrome
- Factors influencing polyautoimmunity
- Does polyautoimmunity influence the severity of autoimmune diseases?
Polyautoimmunity and Severity

Some reports favor severity

- More erosive disease in Rhupus and anti-CCP antibodies
- Higher Incidence of malignancy in RA and SS
- Low rates of remission in MG and AITD
- More severe disease in T1D and celiac disease
- Vasculitis is associated with high SLEDAI score in SLE
- More severity of SLE+APS.

Polyautoimmunity and Severity

Some reports indicate less severity

- Milder disease in MG and AITD
- Milder disease in SSc and AITD
- SS or AITD do not influence outcome in SLE (nephritis)

Marinó et al. J Clin Endocrinol Metab 1997;82:438-43
Avouac et al. J Rheumatol 2010;37:608-14
Rojas-Villarraga et al. Lupus 2010 19: 150
Franco et al. EULAR 2014
Polyautoimmunity

Conclusions

☑ Polyautoimmunity is a frequent condition (10-40%).
☑ Factors associated with polyautoimmunity include gender (female), familial autoimmunity, tobacco smoking, ancestry (amerindian).
☑ Based on polyautoimmunity and depending on severity, autoimmune diseases may be categorized as major and minor conditions. In this sense, how polyautoimmunity affects major autoimmune diseases warrants further investigation.
Polyautoimmunity
Conclusions

✓ The assessment and clustering of polyautoimmunity will help to define plausible approaches to studying the common mechanisms of these diseases (i.e., the autoimmune tautology).

✓ Identification of commonalities among autoimmune diseases may provide insights about salient mechanisms that are necessary and perhaps sufficient for autoimmunity to occur.

✓ Polyautoimmunity, as an extreme phenotype of autoimmunity, would be critical for dissecting genes of major effect conferring susceptibility to autoimmunity.
Rhetoric
From Greek tauto, “the same”; logos, “word/idea”.
*Tautology is an obvious statement.*

Logic
Tautology is a formula, which is true in every possible interpretation.

\[ Vpq = AD1 \sim AD2 \sim AD3 \]

The Autoimmune Tautology
Common mechanisms of autoimmune diseases

- Female predominance
- Shared subphenotypes
- Polyautoimmunity
- Familial aggregation
- Age at onset
- Similar pathophysiology
- Autoimmune ecology
- Ancestry and genetic factors
- Treatment
Shared Subphenotypes Among Autoimmune Diseases

- Clinical
  - Non-erosive arthritis
  - Photosensitivity
  - Raynaud’s phenomenon
  - Alopecia
  - Depression
  - Cardiovascular disease

- Laboratory
  - Antinuclear antibodies
  - Rheumatoid factor
  - Anti-Ro antibodies
Imbalance of Regulatory Cells in Autoimmune Diseases

Th17 Cells in Inflammation and Autoimmunity

Type 1 interferon is a central factor in Autoimmunity

- Presence of IFN signature in autoimmune diseases.
- Regulation of MHC expression.
- Increased amounts of IFN α.
- Activates the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, leading to transcription of IFN-stimulated genes (ISGs).

Epstein–Barr virus and Autoimmune Diseases

IgG anti-EBV

Anaya et al. Autoimmunity. From bench to bedside. 2013
Smoking is a risk factor for autoimmune diseases and their severity

Primary Biliary Cirrhosis

Systemic Lupus Erythematosus

Rheumatoid Arthritis

Autoimmune Thyroid Disease

Multiple Sclerosis

The genetic factors for autoimmune diseases consist of 2 forms: those common to many diseases and those specific for a given disorder.
The Autoimmune Tautology
Common mechanisms of autoimmune diseases

• Female predominance
• Shared subphenotypes
• Polyautoimmunity
• Familial aggregation
• Age at onset
• Similar pathophysiology
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• Ancestry and genetic factors
• Similar treatment
Polyautoimmunity
Conclusions

- Identification of commonalities among ADs may provide insights about salient mechanisms that are necessary and perhaps sufficient for autoimmunity to occur.

- Polyautoimmunity, as an extreme phenotype of autoimmunity, would be critical for dissecting genes of major effect conferring susceptibility to autoimmunity.
Polyautoimmunity Genes

HLA-DRB1, HLA-DQB1, CD226, PTPN22, STAT4, GPR103, TNFAIP3, LRP1/STAT6

The Multiple Autoimmune Syndromes. A Clue for the Autoimmune Tautology

Juan-Manuel Anaya  ·  John Castiblanco  ·  Adriana Rojas-Villarraga  ·  Ricardo Pineda-Tamayo  ·  Roger A. Levy  ·  José Gómez-Puerta  ·  Carlos Dias  ·  Ruben D. Mantilla  ·  Juan Esteban Gallo  ·  Ricard Cervera  ·  Yehuda Shoenfeld  ·  Mauricio Arcos-Burgos

Polyautoimmunity Genes

Novel and rare functional genomic variants in multiple autoimmune syndrome and Sjögren’s syndrome

Angad S Johar1, Claudio Mastronardi1, Adriana Rojas-Villarraga2, Hardip R Patel3, Aaron Chuah3, Kaiman Peng3, Angela Higgins1, Peter Millbum4, Stephanie Palmer5, Maria Fernanda Silva-Lara1, Jorge Ulcedo4, Dan Andrews4, Matthew Field1, Gavin Huntley5, Chris Goodnow5, Juan-Manuel Anaya7 and Mauricio Arcos-Burgos7

Candidate Gene Study in Systemic Sclerosis Identifies a Rare and Functional Variant of the TNFAIP3 Locus as a Risk Factor for Polyautoimmunity

Eugenie Kourmakis,3 Matthieu Giraud,3 Philippe Dieude,3 Vanessa Cohignac,2 Giovanna Cuomo,4 Paolo Airo,5 Eric Hashull,5 Marco Maucci-Cerioni,2 Elizabeth Dion,9 Paola Caramaschi,13 Luc Mouton,10 Valeria Riccieli,11 Jean-Luc Krakowski,13 Kiic Phong Tiev,12 Camille Francès,14 Zahar Amoura,1 Jean Sobilia,15 Anne Cosnes,17 Patrick Carpentier,15 Gabriele Valentini,4 Mirko Munetti,7 Serena Guiducci,1 Olivier Meyer,13 André Kahn,10 Catherine Bollée,20 Gilles Chieocchia,4 and Yannick Allanore3

Genome wide identification of new genes and pathways in patients with both autoimmune thyroiditis and type 1 diabetes

Yaron Tomer 4, b, 5, Lawrence M. Dolan 4, George Kahaly 6, Jasmine Divers 6, Ralph B. D’Agostino Jr. 6, Giuseppina Imperatore 6, Dana Dabelea 6, Santica Marcovina 6, Mary Helen Black 1, Catherine Pihoker 1, Alia Hasham 7, Sara Salehi-Hammarstad 7, David A. Greenberg 8, Yanevi Lotay 1, Wejiga Zhang 1, Maria Cristina Monti 8, Nina Matheis 4, on behalf of the SEARCH for Diabetes in Youth Study
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