Recurrent Infection, Pulmonary Disease, and Autoimmunity as Manifestations of Immune Deficiency

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Disclosures

- Investigator: Boehringer Ingelheim
Learning Objectives

- To understand the interplay between immunodeficiency and allergic and pulmonary disorders.
- To recognize the increasing numbers of monoallelic immune system mutations that have allergic and pulmonary manifestations.
- To incorporate genetic testing in the clinical evaluation of patients with seemingly common diseases.
Hypogammaglobulinemia (Immunodeficiency)

Autoimmunity

Allergy

Hypersensitivity
Host Defense

Specific
- Adaptive immunity

Non-Specific
- Innate immunity
- Barriers
The Innate and Adaptive Immune Response

Pattern recognition receptors

Specific antigen receptors

Primary Immunodeficiency Diseases

Infection  Autoimmunity  Atopy
Malignancy
Primary Immunodeficiency Diseases

Infection
Malignancy
Deficient/defective effector cells

Autoimmunity
Deficient/defective regulatory cells
Primary Immunodeficiency Diseases

Infection \rightarrow Autoimmunity \leftarrow Malignancy

\downarrow \downarrow

Deficient/defective effector cells \rightarrow Deficient/defective regulatory cells
T Cell Receptor Signaling

Signal

Strong

Adaptive IR

Th17

Neutrophilia

Th1

IFNγ

Weak

Atopy

Th1

IgE

Eosinophilia

Th2

Autoimmunity

Absent

Immunodeficiency

Eosinophilia
Pulmonary Complications Associated with PID

• Infectious
  – Bacterial
  – Fungal Viral
  – Opportunistic

• Non-infectious
  – Allergy
  – Autoimmunity
  – Interstitial lung disease (ILD)
    • Granulomatous-lymphocytic ILD (GLILD)
Sinopulmonary Signs Suggesting an Immune Defect

- Recurrent otitis media, sinusitis, bronchitis, and pneumonia with low virulence organisms (*Haemophilus influenza*, *Streptococcus pneumoniae*, *Mycoplasma*, others)
- Unexplained bronchiectasis
- Empyema complicating pneumonia
- Unexplained lung abscess
- Unexplained obstructive lung disease
- Unexplained restrictive lung disease
- Lymphocytic interstitial infiltrates
- Bronchospasm (in nonatopic individuals) with repeated infections
- Granulomatous disease with recurring infections and low immunoglobulins

Survey of JMF Centers

Major Immunodeficiency Groups:

- Predominantly Antibody Deficiencies (n=10078) 53%
- Cellular Immunodeficiencies (n=3713) 20%
- Combined Immunodeficiencies (n=1364) 7%
- Defects of Phagocytic Function (n=1254) 7%
- Disease of Immune Dysregulation (n=606) 3%
- Complement Deficiencies (n=356) 2%
- Defects in Innate Immunity (n=57) 0%
- Other Immunodeficiencies (n=1545) 8%

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Immunodeficiency → Pulmonary → Allergy

Allergy → Pulmonary → Immunodeficiency
Immunodeficiency Diseases with Eosinophilia
Elevated Serum IgE and Eczema
- The Triad –

- Hyper-IgE syndrome (HIES)
- DOCK8 deficiency
Immunodeficiency Diseases with **Eosinophilia**
Elevated Serum **IgE** and **Eczema**
- The Triad –
  and lung disease

- Hyper-IgE syndrome (HIES)
- DOCK8 deficiency
# A Classification of HIES

<table>
<thead>
<tr>
<th>HIES Type</th>
<th>Inheritance</th>
<th>Molecular Genetic Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>• Sporadic (more than 90% of cases) &lt;br&gt;• Familial with autosomal dominant inheritance (rare)</td>
<td>• STAT3 mutations</td>
</tr>
<tr>
<td>Type 2</td>
<td>• Familial with autosomal recessive inheritance &lt;br&gt;• Rare</td>
<td>• TYK2 deficiency</td>
</tr>
</tbody>
</table>
Hyper-IgE (HIES) Syndrome (Job’s Syndrome)

Triad: Cold abscesses, pneumonia, high IgE

• Chronic eczema-like rash/atopic dermatitis
  – Onset - newborn rash
  – Staphylococcal superinfection
• High IgE - often >2,000 IU/mL
• Eosinophilia - usually >700 cells/mL

*Generally free from other allergic manifestations (rhinitis, asthma, urticaria, anaphylaxis). Allergic skin testing usually negative
Hyper-IgE (HIES) Syndrome (Job Syndrome)

- Characteristic facial appearance-coarse features, prominent forehead, broad nasal bridge
- Distinct abnormalities of the connective tissue, skeleton, dentition
- Pneumonia, pneumatoceles
- Mucocutaneous candidiasis
- Coronary and CNS artery aneurysms
- Fractures
- Retained primary teeth
- Scoliosis
- Joint hyperextensibility
Chest Radiograph Showing Right Lower Lobe Infiltrate With Cystic Lesions (Arrow)
Chest CT Scan Showing Extensive Consolidation and Cystic Changes in the Right Lung With Right Pleural Thickening and Left Pleural Effusion With Compressive Atelectasis and Early Infiltrates in the Left Lower Lobe
Immunodeficiency Diseases with Eosinophilia and Elevated Serum IgE

- Hyper IgE syndrome (HIES) AD-HIES
- DOCK8 deficiency AR-HIES
Combined Immunodeficiency Associated With DOCK8 Mutations

• Severe atopy
  – Atopic dermatitis
  – High IgE levels
  – Moderate eosinophilia
  – Food sensitivities
• Otitis media
• Sinusitis
• **Pneumonia**
• Recurrent staphylococcal skin infections with otitis externa
• Recurrent H. simplex/H. zoster
• Molluscum
• Low T, B, and NK cell numbers
• CNS vasculitis*
Clinical Features of DOCK8 Deficiency

- Atopic dermatitis: 91%
- Asthma: 41%
- Allergies: 66%
- High serum IgE: 100%
- Eosinophilia: 90%
- Bacterial skin infections: 78%
- Mucocutaneous candidiasis: 72%
- Any viral infection: HSV, HPV, VZV, MCV: 88%
- Respiratory tract infections: 97%
- CNS vasculitis: 6%
- Malignancy: 19%
- Autoimmune hemolytic anemia: 6%
Common Variable Immunodeficiency Disease (CVID)

**Clinical Manifestations of CVID**

**Infectious Manifestations**
- Pneumonia (atypical and typical organisms)
- Otitis media
- Sinusitis
- Conjunctivitis
- Enteritis

**Noninfectious Manifestations**
- Autoimmune cytopenias
- Granulomatous disease
  - Lymphadenopathy
  - Splenomegaly
  - Enteropathy
  - Nodular regenerative hyperplasia
  - Polyarthritis
  - Interstitial lung disease/GLILD
  - Malignancy (lymphoma/MALToma)
Clinical and Laboratory Criteria for Diagnosis of CVID

Clinical criteria for a probable diagnosis
At least one of the following:
• Increased susceptibility to infection
• Autoimmune manifestations
• Granulomatous disease
• Unexplained polyclonal lymphoproliferation
• Affected family member with antibody deficiency

Laboratory criteria for a probable diagnosis
- Marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2SD of the age-normal levels AND at least one of the following:
• Poor antibody response to vaccines (and/or absent isoahaemagglutinins); i.e. absence of protective levels despite vaccination where defined
• Low switched memory B cells (<70% of age-related normal value)
GLILD

- Lymphocytic interstitial pneumonia (LIP)
- Follicular bronchiolitis
- Granulomatous lung disease
- Organizing pneumonia
Silent Radiological Features of GLILD

- **Plain X-ray**
  - Diffuse interstitial infiltrates

- **HRCT**
  - Consolidation
  - Ground glass opacities
  - Reticular abnormalities
Imaging in Common Variable Immunodeficiency
Bronchiectasis

- Most common radiologic abnormality in CVID (25-73%), usually in lower lobes
- Associated with mucous plugging and tree-in-bud nodules
- Bronchiectasis is related to history of recurrent infections
- Bronchiectasis is rare in young patients. Prevalence increases over time, correlating to number of infections
- However, presence of bronchiectasis does not correlate with IgG levels
Granulomatous Lymphocytic Interstitial Lung Disease (GLILD)

- GLILD is a unique entity, occurring only in the setting of CVID and CVID-like illnesses
- Mixed restrictive/obstructive physiology
- Associated with a poorer prognosis than CVID without GLILD

Pathology
- Non-necrotizing granulomas
- LIP
- FB
- Lymphocyte hyperplasia
- MALToma

GLILD - Pathology

Nodular dense lymphoid hyperplasia. Underlying architecture is preserved.

Non-necrotizing granuloma
Characterized uniquely by a combination of ground glass and consolidative opacities with septal thickening, nodularity, and adenopathy

Usually lower lung predominant, often peribronchovascular in distribution

May progress to fibrosis

Radiologic findings may wax and wane over time
Lymphoproliferative Disease in CVID

- Increased risk of lymphoma up to 30x
- Most commonly non-Hodgkin lymphoma, B-cell subtype
- Often extra-nodal and associated with mucosal tissues
- MALT (mucosa-associated lymphoid tissue) lymphoma or MALToma, a subset of B-cell non-Hodgkin lymphoma

Lymphocytic infiltration in pulmonary MALToma effaces the normal architecture, destroying the bronchiole (arrows)
## Comparison of Initial Clinical and Laboratory Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Progressive (n = 9)</th>
<th>Stable (n = 6)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (y)</td>
<td>45</td>
<td>45</td>
<td>.38</td>
</tr>
<tr>
<td>Female (%)</td>
<td>3 (33)</td>
<td>4 (67)</td>
<td>.32</td>
</tr>
<tr>
<td>CT-confirmed bronchiectasis (%)</td>
<td>4 (44)</td>
<td>4 (67)</td>
<td>.61</td>
</tr>
<tr>
<td>History of ITP (%)</td>
<td>8 (89)</td>
<td>2 (33)</td>
<td>.09</td>
</tr>
<tr>
<td>History of splenomegaly (%)</td>
<td>9 (100)</td>
<td>5 (83)</td>
<td>.40</td>
</tr>
<tr>
<td>History of lymphadenopathy (%)</td>
<td>8 (89)</td>
<td>2 (33)</td>
<td>.09</td>
</tr>
<tr>
<td>History of NRH or chronic noninfectious hepatitis (%)</td>
<td>4 (44)</td>
<td>0 (0)</td>
<td>.10</td>
</tr>
</tbody>
</table>
Univariate Analyses of Granulomatous Lymphocytic Interstitial Lung Disease Predictors

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytopenia</td>
<td>26.62</td>
<td>6.63–181.40</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypersplenism</td>
<td>31.91</td>
<td>10.05–120.87</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>4.91</td>
<td>1.43–19.75</td>
<td>0.01</td>
</tr>
<tr>
<td>Dyspnea score*</td>
<td>1.77</td>
<td>1.31–2.55</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Dosage IVIG†</td>
<td>1.01</td>
<td>1.01–1.07</td>
<td>0.01</td>
</tr>
<tr>
<td>IgA‡</td>
<td>0.95</td>
<td>0.89–0.98</td>
<td>0.01</td>
</tr>
<tr>
<td>IgE</td>
<td>0.99</td>
<td>0.96–1.00</td>
<td>0.09</td>
</tr>
<tr>
<td>IgG‡</td>
<td>0.99</td>
<td>0.98–0.99</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IgM</td>
<td>0.99</td>
<td>0.97–1.00</td>
<td>0.09</td>
</tr>
<tr>
<td>IgD⁺CD27⁺ B cells,§ %</td>
<td>0.95</td>
<td>0.90–0.99</td>
<td>0.02</td>
</tr>
<tr>
<td>IgD⁻CD27⁺ B cells,§ %</td>
<td>0.91</td>
<td>0.82–0.99</td>
<td>0.02</td>
</tr>
<tr>
<td>FVC % predicted∥</td>
<td>0.96</td>
<td>0.93–0.98</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FEV₁, % predicted∥</td>
<td>0.96</td>
<td>0.94–0.99</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>D_LCO % predicted∥</td>
<td>0.92</td>
<td>0.88–0.95</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Treatment Options in GLILD

- IVIG
- Corticosteroids
- Azathioprine
- Rituximab
- Mycophenolate
- TNF antagonists
- Cyclosporine
Granulomatous (non-necrotizing) Disease

- T cells
- B cells
- Follicles with germinal centers
KEY POINTS

- **GATA2** deficiency has variable presentations including infections, multilineage cytopenias, MDS/AML, lymphedema, aplastic anemia and pulmonary alveolar proteinosis.

- **GATA2** mutations occur throughout the gene (exons, introns, regulatory) leading to haploinsufficiency and dysregulation of a critical transcription factor network.

- HSCT reverses the infectious, hematopoietic and pulmonary disease seen in GATA2 deficiency.
## Mendelian Immune Disorders Predisposing to Mycobacterial Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Form/Molecular Basis</th>
<th>Mycobacterium sp</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSMD</strong></td>
<td><strong>Response to IFN(\gamma) abolished:</strong></td>
<td>BCG</td>
</tr>
<tr>
<td></td>
<td>c-AR-IFN(\gamma)-R1 deficiency</td>
<td>M. avium, kansasii</td>
</tr>
<tr>
<td></td>
<td>c-AR-IFN(\gamma)-R2 deficiency</td>
<td>M. szulzai, cheloneae, fortuitum, abscessus, smegmatis, peregrinum</td>
</tr>
<tr>
<td></td>
<td><strong>Impaired response to IFN(\gamma):</strong></td>
<td>BCG</td>
</tr>
<tr>
<td></td>
<td>p-AR-IFN(\gamma)-R1 deficiency</td>
<td>M. avium, kansasii</td>
</tr>
<tr>
<td></td>
<td>p-AD-IFN(\gamma)-R1 deficiency</td>
<td>M. cheloneae, abscessus</td>
</tr>
<tr>
<td></td>
<td>p-AR-IFN(\gamma)-R2 deficiency</td>
<td>M. gorvonac, asiaticum</td>
</tr>
<tr>
<td></td>
<td>p-AD-STAT1 deficiency</td>
<td>M. tuberculosis</td>
</tr>
<tr>
<td></td>
<td><strong>Impaired IFN(\gamma) production:</strong></td>
<td>BCG</td>
</tr>
<tr>
<td></td>
<td>c-AR-IL-12R(\beta)1 deficiency</td>
<td>M. avium, cheloneae</td>
</tr>
<tr>
<td></td>
<td>c-AR-IL-12p40 deficiency</td>
<td>M. tuberculosis</td>
</tr>
</tbody>
</table>
Fig. 2. Cells producing and responding to IFN-γ. Proteins for which mutations in the corresponding genes have been identified and associated with Mendelian susceptibility to mycobacterial disease (MSMD) are indicated in blue. The allelic heterogeneity of nine genes results in the definition of 18 genetic disorders. MSMD-causing mutations of IFNGR1, IFNGR2, STAT1, IRF8 and CYBB impair the action of IFN-γ. MSMD-causing mutations of IL12B, IL12RB1, ISG15, IRF8 and NEMO impair the production of IFN-γ.
Fig. 3. Distribution of genetic disorders in MSMD patients with known etiologies. The genetic defects observed in 406 MSMD patients with known mutations are shown. The proportions of complete recessive (CR), partial recessive (PR), and partial dominant (PD) defects of autosomal genes (IFNGR1, IFNGR2, STAT1, IRF8, IL12B, IL12RB1 and ISG15), and X-linked recessive (XR) genes (NEMO and CYBB) are indicated.
Fig. 4. Infections in patients with deficiencies of IFN-γR and STAT1. Infections in 115 patients with IFN-γR1 deficiencies (complete and partial), 21 patients with IFN-γR2 deficiencies (complete and partial) and 17 reported patients with partial dominant STAT1 deficiency. Some patients had multiple episodes of infectious diseases. BCG: bacillus Calmette-Guérin, EM: environmental mycobacteria.
Fig. 5. Infections in patients with IL-12Rβ1 and IL-12p40 deficiencies. Infections in 180 patients with complete IL-12Rβ1 deficiency and in 50 reported patients with complete IL-12p40 deficiency. Some patients had multiple episodes of infectious diseases. BCG: bacillus Calmette-Guérin, EM: environmental mycobacteria.
Anticytokine AAbs and Disease Associations

# Monogenic Defects Presenting With Antibody Deficiency, Autoimmunity, and Pulmonary Manifestations

<table>
<thead>
<tr>
<th>Gene Product</th>
<th>Antibody Deficiency</th>
<th>Autoimmunity</th>
<th>Pulmonary</th>
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<tbody>
<tr>
<td>Thymic Selection/Tregs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTLA4</td>
<td>B-cell defects</td>
<td>+</td>
<td>LIP</td>
</tr>
<tr>
<td>LRBA</td>
<td></td>
<td>+</td>
<td>Bronchiectasis/EBV-LIP</td>
</tr>
<tr>
<td>Signaling Pathways</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITK</td>
<td>+</td>
<td>+</td>
<td>Nodules</td>
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<tr>
<td>NF-κB Signaling</td>
<td></td>
<td>+</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>NF-κB1</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>STAT Signaling</td>
<td></td>
<td></td>
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<tr>
<td>STAT3 GOF</td>
<td>+</td>
<td>+</td>
<td>Mycobacteria</td>
</tr>
<tr>
<td>TAC1</td>
<td>+</td>
<td>+</td>
<td>GLILD</td>
</tr>
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</table>